JUNE 1953

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

ABBIE I. KNOWLTON

DEWITT STETTEN, JR.

JOSEPH B. KIRSNER

LAWRENCE W. SLOAN

On Qualifications for School Medical Director
Statement Prepared by
The Committee on Public Health Relations

76.6% of patients preferred

EURAX® CREAM...

for relief of 76.6% pruritus

In a recent study[1] of 200 cases of itching dermatoses, 76.6% of all patients who had had previous experience with other antipruritics expressed a preference for EURAX Cream.

In this study, as in previous reports[2-6], EURAX Cream produced complete relief of itching in approximately 65 per cent of cases, and partial relief in most of the remainder.

Other favorable features of EURAX Cream that were again confirmed include:

- ✓ *Prolonged effect lasting up to 8 hours or more.*
- ✓ *No loss of effect on continued use.*
- ✓ *Virtually complete lack of sensitizing or toxic properties.*

EURAX... not an antihistaminic or a -caine derivative... is indicated for prompt, prolonged relief of itch in practically all forms of dermatosis including pruritus due to administration of antibiotics.

EURAX Cream® (brand of crotamiton cream) contains 10% N-ethyl-o-crotonotoluide in a vanishing-cream base. Tubes of 20 Gm. and 60 Gm. and jars of 1 lb. at your local pharmacy.

Bibliography

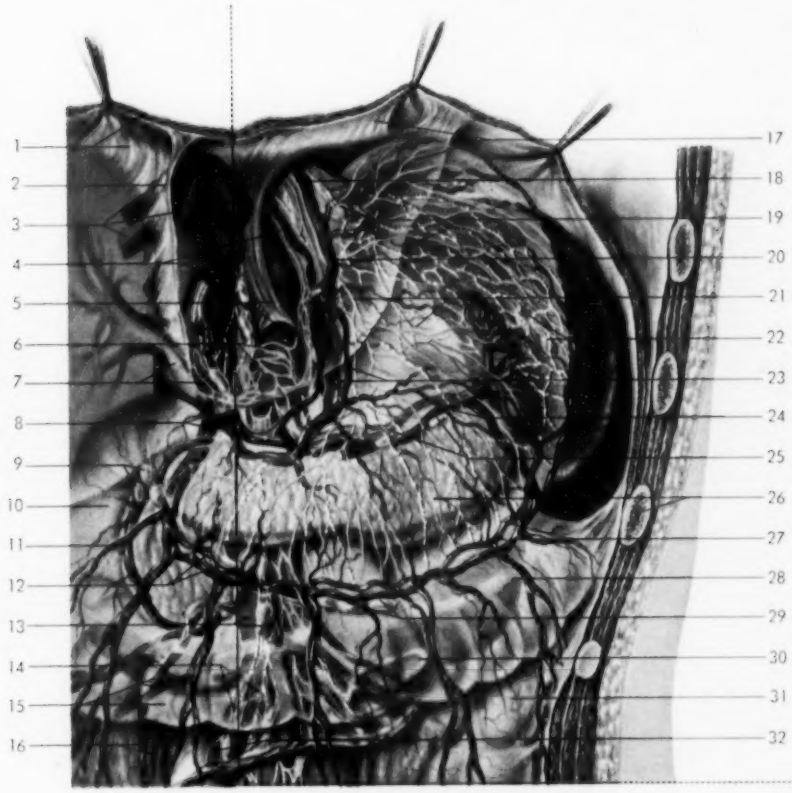
1. Rhett, J. M., South Carolina M. J. (1958), 1954.
2. Peck, S. M., and Hinkelfinger, T. J.: New York State J. Med. 56:1370, 1956.
3. Cronemeyer, M. J.: Internat. Dermatol. 12:65, 1958.
4. Bodin, A.: Quart. Rev. Int. Med. & Dermat. 2:1, 1951.
5. Johnson, S. M., and Reiner, J. W.: Arch. Dermatol. & Syph. 67:703, 1953.
6. U.S. Pat. 2,711,351.

Samples and Reprints on Request

Geigy

GEIGY PHARMACEUTICALS
Division of Geigy Co., Inc.
220 Church St., New York 13, N. Y.

Upper Left Quadrant of the Abdomen



1 Diaphragm and coronary ligament
2 Falciform ligament
3 Hepatic veins
4 Inferior vena cava and right vagus nerve
5 Crus of diaphragm and abdominal aorta
6 Celiac artery and celiac plexus
7 Hepatic artery and portal vein
8 Gastroduodenal artery and vein
9 Subpyloric lymph nodes
10 Duodenum
11 Superior pancreaticoduodenal artery and vein
12 Right gastroepiploic artery and vein
13 Superior mesenteric artery and vein
14 Superior mesenteric lymph nodes
15 Transverse colon and right colic artery and vein
16 Spermatic artery and vein
17 Left triangular ligament and left lobe of liver
18 Esophagus and left vagus nerve
19 Paracardial lymph nodes
20 Esophageal branch of left gastric artery and vein
21 Gastric rami of vagus nerve
22 Splenic lymph nodes
23 Left gastric artery and coronary vein
24 Spleen and splenic artery and vein
25 Superior pancreatic lymph nodes
26 Pancreas and tenth rib
27 Left gastroepiploic artery and vein
28 Left kidney
29 Inferior gastric lymph nodes
30 Jejunum
31 Descending colon
32 Ileocolic artery and vein

This is one of a series of paintings for Lederle by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where aureomycin may prove useful.

Lederle

In peritonitis,
in intestinal infections,
and as a prophylactic adjunct
in surgery of the bowel—

Aureomycin

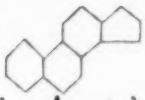
HYDROCHLORIDE CRYSTALLINE

provides an unsurpassed
range of antimicrobial action

Literature available on request

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY
30 ROCKEFELLER PLAZA, NEW YORK 20, N. Y.

cortisone + SCHERING = Cortogen

the symbol SCHERING denotes leadership in steroid hormone  research and manufacture -- including Cortogen in the most useful clinical forms. For systemic therapy, use Cortogen tablets SCHERING or injection . For eye disorders use Cortogen ophthalmic suspension -- sterile . The Schering seal SCHERING appears on each tablet and package -- your assurance of quality.

CORTOGEN®

Acetate (cortisone acetate, Schering) Tablets, 5 mg. and 25 mg.;
Injection, 25 mg. per cc., 10 cc. multiple-dose vials;
Ophthalmic Suspension—*Sterile*, 0.5% and 2.5%, 5 cc. dropper bottles.

Schering CORPORATION · BLOOMFIELD, NEW JERSEY
In Canada: Schering Corporation, Ltd., Montreal

CORTOGEN

SCHERING

Gantrisin 'Roche'

antibacterial action plus...

greater solubility

Gantrisin is a sulfonamide so soluble that there is little danger of renal blocking and little or no need for alkalinization.

high blood level

Gantrisin not only produces a high blood level but also provides a wide antibacterial spectrum.

economy

Gantrisin is a relatively economical antibacterial agent.

less sensitization

Gantrisin is a single drug—not a mixture of several compounds of fundamentally unrelated chemical structure—so that there is less likelihood of sensitization.

GANTRISIN®—brand of sulfisoxazole
(3,4-dimethyl-5-sulfanilamido-isoxazole)

TABLETS • AMPULS • SYRUP

HOFFMANN-LA ROCHE INC.

Roche Park • Nutley 10 • New Jersey

The Bulletin of The New York Academy of Medicine, Vol. 29, No. 6. Published Monthly by The New York Academy of Medicine, 2 East 103 Street, New York 29, N. Y. Entered as second-class matter February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Subscription, Domestic and Foreign copies, $5.00. Single copies, 50c.

Early Recognition of Peripheral Vascular Disease is Frequently Limb Saving

THE U. M. A. THERMOCOUPLE IS INVALUABLE FOR TAKING SURFACE AND INTRAMUSCULAR TEMPERATURES:

1 To accurately and rapidly determine the efficacy of vasodilating drugs.

2 Most sensitive instrument for the purpose. Simple to use — Direct readings with no calculations.

This valuable instrument is now available on an inexpensive rental plan:

- $6.00 per month — Keep it or return it whenever you please.
- Rent it for 24 months and it belongs to you.
- No interest, service charge or red tape.
- Order it and we will deliver or ship it immediately to any part of the United States.

•

U. M. A. INCORPORATED

56 COOPER SQUARE
New York 3, N. Y.
ALgonquin 4-0924

NO. 3 OF A SERIES OF MESSAGES PRESENTED AS A SERVICE TO THE PROFESSION BY THE AMERICAN CHLOROPHYLL DIVISION OF STRONG COBB & CO. INC., FIRST COMMERCIAL PRODUCERS OF A CHEMICALLY MEASURABLE WATER-SOLUBLE EXTRACT, 1933.

Based on the Brochure—"Chlorophyll 1953" by Walter H. Eddy, Ph.D.

Scientific Facts on CHLOROPHYLL

ODOR-COMBATTING POWER of chlorophyll derivatives was first noted as a side effect during studies on wound healing. In 1940, Gruskin[1] focussed attention on the deodorant power of chlorophyllins in wound therapy when, reporting on 1200 varied infections, he observed that "prompt disappearance of odor was noted," even in cases of ulcerative carcinoma with extensive putrefaction and in other foul smelling lesions.

Reporting on 400 patients, many of whom had compound fractures with osteomyelitis which "were so malodorous as to deprive both patients and attendants of appetite," Bowers[2] says, "Our first observation on beginning use of chlorophyll was that this odor immediately disappeared."

In recognition of the marked deodorizing potency of topically applied chlorophyll derivatives, the Reference Committee of the Council of Chemistry and Pharmacy of the American Medical Association[3] said, "Chlorophyll was found consistently to be an effective deodorant when used in foul smelling wounds."

These reports stimulated study of the possibilities of chlorophyllins as systemic deodorants when used internally. In colostomies, Goodman[4] reports that attending fecal odors can be eliminated for several hours by inserting a capsule containing chlorophyllin and kaolin within the colostomy immediately after the morning irrigation and evacuation. Joseph[5] controlled fecal odors in colostomy, intestinal fistulae, and bedridden patients on a regimen starting with two chlorophyllin tablets four times a day.

Taber[6] completely eliminated lochial and menstrual odors in a high percentage of women tested by divided doses of four chlorophyllin tablets daily. Deodorization lasted five to twelve hours after last dose.

The response of normal body and breath odors to chlorophyllins, either topically or internally, has attracted perhaps the widest popular interest. Tebrock[7] tested 567 subjects in an industrial plant. Subjects took two chlorophyllin tablets daily and observed usual personal hygiene but used no other deodorants. In 86% breath odor was helped, in 62% foot odor relieved, in 66% menstrual odor obliterated, and in 78% perspiration odor benefited.

Deodorant qualities of chlorophyll derivatives are today seldom questioned. Finer measurement, identification and standardization of chlorophyll derivatives are in progress in research laboratories throughout the United States. American Chlorophyll is as proud to be a part of this scientific development as it is to have been the first to produce water-soluble chemically-measurable chlorophyllins as far back as 1933.

1. Gruskin, B., Am. J. Surgery 49:49, 1940.
2. Bowers, W. F., Am. J. Surgery 73:37, 1947.
3. Moss, N. H., Morrow, B. A., Long, E. C., Ravdin, I., J.A.M.A. 140:1336, 1949.
4. Goodman, J. M., Surgery 28:550, 1950.
5. Joseph, M., West. J. Surg., Ob. & Gyn., 60:363, 1952.
6. Taber, F. S., J. Med. Soc. of N. J. 48:321, 1951.
7. Tebrock, S., Proc. Sci. Sec. Proprietary Assn. Dec. 7, 1951.

AMERICAN CHLOROPHYLL DIVISION

STRONG COBB & CO. INC.
LAKE WORTH, FLORIDA

ETHICON®
SURGICAL
SUTURES

to prevent attacks in angina pectoris

4 out of 5 patients respond in 3 studies

The consistency with which Peritrate can prevent attacks in angina pectoris is demonstrated in the published reports of three investigators. Each obtained good results in almost the same high percentage of patients:

Humphreys *et al.*[1]..*78.4% had fewer attacks*
Plotz[2].....*80% had fewer attacks*
Dailheu[3].....*80% had fewer attacks*

Used as a prophylactic agent—rather than to provide relief when an attack is present or imminent—Peritrate will in many cases

- **reduce the number of attacks**
- **reduce the severity of attacks which are not prevented**

Other beneficial effects:

Extensive clinical use has demonstrated that, in addition to preventing or minimizing attacks, Peritrate will frequently

- **reduce the nitroglycerin requirement**
- **increase exercise tolerance**
- **improve the EKG picture**

For effective prophylactic management

A long-lasting coronary vasodilator, Peritrate provides prophylactic action for 4 to 5 hours. Administration must be maintained on a continuing daily schedule—usually one tablet 3 or 4 times daily. Some patients will require a 2-tablet dose. Peritrate is available in 10 mg. tablets in bottles of 100, 500 and 5000.

1. Humphreys, P., *et al.*: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: N. Y. State J. Med. 52:2012 (Aug. 15) 1952.
3. Dailheu-Geoffroy, P.: L'Ouest-Méd., vol. 3 (July) 1950.

Peritrate®

TETRANITRATE

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT
Laboratories NEW YORK

for low-sodium dieters

de gustibus...

By direct appeal to the palate, DIASAL enlists the willing cooperation of patients on low-sodium diets. Its exceptionally high taste-equivalence to table salt is matched by close resemblance in other properties[1] — DIASAL looks, pours and otherwise behaves like sodium chloride at the table and in the kitchen. Containing chiefly potassium chloride (plus glutamic acid and inert excipients), DIASAL is free from sodium, lithium and ammonium. It is accordingly safe to prescribe for prolonged and liberal use. DIASAL also serves as a prophylactic against the potassium depletion which may accompany low-sodium dieting[2]

DIASAL FOUGERA

seasons food like salt safely

packaging: available in 2-oz. shakers and 8-oz. bottles.

Samples and low-sodium-diet sheets for your patients available on request to Professional Service Department.

FOUGERA

E. FOUGERA & COMPANY, INC.
75 VARICK STREET, NEW YORK 13, N. Y.

1. Rimmerman, A. B., and others: A Comparative Study of Sodium-free Salt Substitutes, Am. Pract. & Digest Treat. 2:158, 1951.
2. Fremont, R. E., and others: Postgrad. Med. 10:216, 1951.

IN ANY ALLERGY

'Co-Pyronil' *

affords

more profound,

more prolonged

relief with

fewer side-effects

than any other

known

antihistaminic.

*'Co-Pyronil' (Pyrobutamine Compound, Lilly)

Dosage

Mild symptoms: 1 pulvule every twelve hours.

Moderate symptoms: 1 pulvule every eight hours.

Severe symptoms: 2 pulvules every eight hours.

Lilly

SECOND SERIES JUNE 1953 VOL. 29, NO. 6

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

Cushing's Syndrome 441
Abbie I. Knowlton

Metabolic Effects of Insulin 466
DeWitt Stetten, Jr.

Hormones and Peptic Ulcer 477
Joseph B. Kirsner

Eye Changes in Relationship to Disorders of Thyroid Function 505
Lawrence W. Sloan

On Qualifications for School Medical Director . . . 518
Statement Prepared by The Committee on Public Health Relations

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

ADVERTISING OFFICE • 30 ROCKEFELLER PLAZA, N. Y. C. 20 • CIRCLE 7-7706

Copyright, 1953 by The New York Academy of Medicine

OFFICERS AND STAFF OF THE ACADEMY

1953

President

ALEXANDER T. MARTIN

Vice-Presidents

HENRY ALSOP RILEY — EDWARD J. DONOVAN — CLAUDE E. FORKNER

Treasurer

SHEPARD KRECH

Recording Secretary

FREDERICK H. WILKE

Trustees

GEORGE BAEHR — FRANK B. BERRY — ARTHUR F. CHACE — BRADLEY L. COLEY — CONDICT W. CUTLER, JR. — *SHEPARD KRECH — ASA L. LINCOLN — *ALEXANDER T. MARTIN — HAROLD R. MIXSELL — WILLIAM BARCLAY PARSONS — BENJAMIN P. WATSON — ORRIN S. WIGHTMAN — *FREDERICK H. WILKE

Council

The President — The Vice-Presidents — The Trustees
The Treasurer — The Recording Secretary
The Chairmen of Standing Committees

Director

HOWARD REID CRAIG

Librarian

JANET DOE

Executive Secretary
Public Health Relations Committee

HARRY D. KRUSE

Executive Secretary
Committee on Medical Education

ROBERT L. CRAIG

Executive Secretary
Committee on Medical Information

IAGO GALDSTON

Comptroller

ARTHUR A. EBERLE

Legal Counsel

JOHN W. DAVIS, ESQ.

Library Consultants

B. W. WEINBERGER, CURT PROSKAUER

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman*
DAVID P. BARR
WILLIAM DOCK
JANET DOE
JOHN G. KIDD
LEILA CHARLTON KNOX
ROBERT F. LOEB
LOUIS M. ROUSSELOT

ROBERT L. CRAIG, *Secretary and Editor*

---

* Ex-officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 29, NO. 6 JUNE 1953

CUSHING'S SYNDROME*

ABBIE I. KNOWLTON

Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University

INTRODUCTION

FIRST of all, I want to say that I feel greatly honored to be one of the speakers participating in the Graduate Fortnight.

Cushing's syndrome, which is the subject under discussion, is a disease which has intrigued the neurosurgeons, endocrinologists and pathologists for years. Much of the interest in this entity has centered around the question as to whether the pituitary, the adrenal cortex or even the hypothalamus is the site of the initial lesion, though it is generally agreed that the end result is due to excess activity of the adrenal cortical hormones.

Recently the disease has attracted the attention of physicians in general due to the fact that this spontaneous form of hyperadrenalism invites comparison with the similar condition induced by long-term treatment with ACTH or cortisone. The earliest reports on the use of these substances drew attention to the Cushing-like features which the patients receiving them developed and as time has passed, each of the wide vari-

* Presented at the 25th Graduate Fortnight of The New York Academy of Medicine, October 13, 1952. From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York.

TABLE I—SYMPTOMS AND SIGNS FREQUENTLY ENCOUNTERED IN CUSHING'S SYNDROME

	Columbia Series (38 patients)	*Reports from literature (189 patients)*
	per cent	*per cent*
Obesity—truncal and facial	95	97
plethoric appearance	85	50
dermatological abnormalities	82	26
Hypertension	92	85
Disturbances in gonadal function, amenorrhea, oligomenorrhea, impotence	86	71
virilism	6	5
Hirsutism	76	69
Purple striae	69	71
Weakness and backache	68	50
Mental abnormalities	66	31
minor 40		
major 26		
Purpura, easy bruising	58	23
Poor wound healing or severe infections	42	30
Headache	40	34

ety of abnormalities seen in the spontaneous disease has been encountered in the group of steroid-treated patients. This similarity between the two conditions has stimulated interest in the natural history of Cushing's syndrome, and brought out the fact that although case reports abound, in no place has a large enough group of patients been collected to provide satisfactory data on the general course of the disease.

In order to provide such information, Dr. Charles Plotz, Dr. Charles Ragan and myself have reviewed the thirty-three patients with Cushing's syndrome who have been studied during the past twenty years at the Columbia-Presbyterian Medical Center. Since this number afforded a relatively small group from which to draw conclusions as to the overall picture of the disease, an additional 189 cases were collected from the literature. This combined group has recently been reported.[1] Since its completion, an additional five patients have come under our observation, and these have been added to the above series to form the basis

of the clinical material for this evening's discussion. In gathering this group of patients an effort was made to include only unequivocal examples of the syndrome and to obtain as long periods of observation as possible. In the Columbia patients, only one has been lost to follow-up; the remaining thirty-seven have been seen for periods ranging from a few months to twenty years.

Clinical Picture

There have been so many presentations of the clinical picture of Cushing's syndrome that to add yet another would be redundant, and indeed considering the excellence of the descriptions already available, it would be presumptuous. Hence I shall touch on this aspect only to compare the findings in the present series with those previously reported. As is well recognized, this disease is primarily one of young adults; the average age of onset in the Presbyterian Hospital group was twenty-nine, with the youngest patient being eleven and the oldest fifty-five. The fact that thirty of the thirty-eight patients were women is in keeping with the known preponderance in this sex. Only one instance of the occurrence of Cushing's disease in a Negro was found in the literature; however, three such patients were encountered in the present group. The more common symptoms and signs which have been seen in patients with Cushing's syndrome are summarized in Table I. The patients comprising the present series have been considered separately from the larger group gathered from the literature. In general the agreement between the two groups is excellent, but certain differences exist upon which I shall comment.

Obesity remains the hallmark of the syndrome, but the use of this term "obesity" requires amplification. It is true that the majority of patients gave a history of impressive weight gain; however, a certain proportion had no change in weight or sustained an actual loss. In each instance, whatever the overall change, there was a redistribution of tissue to give the characteristic facial and truncal obesity. Only one patient of the present series complained of discomfort in relation to the disposition of fat, hence the feature, "painful obesity," mentioned in Cushing's original paper,[2] would seem to be relatively uncommon. In conjunction with the rounding of the face, the great majority exhibited reddening or a dusky cyanosis about the head and neck. Dermatological abnormalities were seen very frequently in the present group; their much lower

incidence in the larger group gathered from the literature may well be due to the fact that, being a minor symptom, it was often not deemed worthy of recording. It is interesting to note, however, that one of the earliest and most completely described instances of Cushing's was reported in the dermatological literature in 1926. That is the case of Parkes-Weber which Cushing included in his original report. The type of skin lesions showed great variety, the most common being acne, fungal infections and patches of pigmentation.

High on the list of findings stands hypertension, and in general this was marked by impressively high diastolic levels. Considering the severity of the hypertension, it was remarkable to note its complete reversibility in patients in whom remissions occurred. This held true even though the blood pressure had been elevated for years. It is also surprising that fundoscopic abnormalities of note were described in only five of the thirty-four patients in whom the eye-grounds were examined.

Suppression of gonadal function was recorded routinely in these patients with Cushing's syndrome – impotence in men and amenorrhea or at least oligomenorrhea in women. However, gonadal function at times was surprisingly normal. An example of this among the present group was a patient, first seen in 1945 with symptoms suggestive of Cushing's syndrome, and readmitted four years later with evident progression of her disease. At this latter time she had severe hypertension, plethora, purple striae, diabetes, osteoporosis with wedging of one vertebra and amenorrhea. However, the amenorrhea proved to be secondary to a six months pregnancy! Dr. Ann Forbes has written us of another such instance where pregnancy became established while a patient was definitely hyperadrenal. Even where marked suppression of menstrual function existed, virilization was rarely seen and this distinguishes the Cushing group from patients with the adrenogenital syndrome. In the Columbia series of patients, enlargement of the clitoris was noted in only two of the women patients, and in none was the body configuration or voice masculine. It is true that hirsutism developed in the majority. Although this usually included the appearance in the women of facial hair over the moustache and beard areas, these sites were rarely the only ones involved. More commonly the entire face was covered with a fine lanugo-like hair including not only the upper lip and chin but also the cheeks and even the forehead. Similar hair frequently covered much of the body.

Of the various signs associated with the syndrome, certainly the occurrence of purple striae is the most useful diagnostically. While striae may develop under any situation in which the skin is rapidly stretched, the bright red or purple type are peculiar to this syndrome. Although such striae were found in the majority of the patients, a significant proportion remained in which this helpful diagnostic sign was lacking. Weakness and backache were noted as frequently as was the occurrence of striae, but their non-specificity of character rendered these symptoms far less useful diagnostically. In a few instances weakness dominated the clinical picture, suggesting a primary muscle-wasting disease. It is interesting that backache, although at times in association with compression fractures of the spine, was never incapacitating.

Up to this point the agreement between the cases of the present series and those gathered from the literature has been fairly good. In the incidence of mental abnormalities, however, there is considerable discrepancy. The reason for this is not clear unless it be related to the generally longer follow-up available in the present series, during which there was more time for these abnormalities to become manifest. In the present group, abnormal reactions have occurred with disturbing frequency. In the milder forms, the disturbance might be no more than that the patient was emotionally labile, uncooperative and presented a difficult problem in ward management. However, nine patients, or 26 per cent, had major mental disturbances. The types of abnormality varied widely and included depressions, paranoid reactions and confused states. One attempted suicide; six became so acutely disturbed that it was necessary to transfer them to institutions for specific psychiatric treatment. The uniform clearing of the mental picture in the event of a remission in the other aspects of the disease was strong evidence for an intimate relationship between the psychic abnormality and the metabolic disturbance. However, when the metabolic abnormality persisted, no prediction could be made as to the appearance, intensity or persistence of the mental abnormality. For example: in one patient the disease progressed to death with no evidence of abnormal mental response during the entire course; in another, the onset of abnormal behavior paralleled the progression of other signs of hyperadrenalism; in a third, a sudden psychotic episode appeared after the physiological stigma of the syndrome had been present but not progressive for more than a year; while in still a fourth, an acute paranoid psychosis, which had

necessitated psychiatric hospitalization, cleared sufficiently to permit the patient to resume her life at home despite the fact that the other features of hyperadrenalism progressed relentlessly until her death in cardiac failure a year later.

Purpura and easy bruisability were remarked upon in the majority of patients in the Presbyterian Hospital series. Why the spontaneous type of hyperadrenalism is accompanied by a bleeding tendency, while ACTH and cortisone have proved of some value in the treatment of such conditions, is wholly unknown.

The incidence of poor wound healing or of unusual infections was alarmingly high in both groups of cases reviewed.

A significant number of patients complained of severe and protracted headaches. In the present series, no correlation existed between this symptom and other evidence of neurological disease. It so happened that the three patients subsequently proven to have adenomata of the pituitary – one had a basophilic adenoma and the other two each had a chromophobe adenoma–were not troubled with severe headaches, while this symptom was particularly severe in three patients with benign adrenal tumors and in one suffering from an adrenal carcinoma.

Of this group of symptoms and signs, the almost universal hypertension, the frequently abnormal mental reactions and the likelihood of poor wound healing or of unusual infections stand out as the three most serious and as real threats to the life of the patient with Cushing's syndrome. Their high incidence in the spontaneously occurring form of the disease suggests that similar difficulties might be anticipated in patients under prolonged treatment with ACTH or cortisone. It is fortunate that, during such therapy, hypertension has developed with much less frequency than in Cushing's syndrome, and has been limited chiefly to patients with underlying renal disease, as pointed out in a recent article by Dr. George Perera.[3] On the other hand, the appearance of abnormal mental reactions and the insidious development and serious nature of intercurrent infections, although less common than in Cushing's syndrome, have been among the chief concerns in patient management on ACTH or cortisone.

Laboratory Data and X-ray Findings

An analysis of the laboratory data from the cases reported from the literature proved to be difficult, due to the fact that the amount of data

TABLE II—FREQUENTLY ABNORMAL LABORATORY AND X-RAY FINDINGS IN CUSHING'S SYNDROME

(Columbia series—38 patients)

	Per Cent Abnormal	*Average*	*Range*
Diminished carbohydrate tolerance (31)	94		
overt diabetes	24		
fasting blood sugar mg.%		116	61-300
X-ray evidence of demineralization			
spine (35)	74		
skull (36)	50		
compression fractures of spine (35)	34		
rib fractures	11		
Increased 24-hr. excretion of "corticoids" (10)	70		
Formaldehydrogenic method (7)		3.0	0.9-7.7
(normal 1-2 mg/24 hr.)			
Phosphomolybdic acid method (3)		7.0	4.1-9.9
(normal 2-4 mg/24 hr.)			

varied greatly from case to case and the laboratory techniques employed were often not comparable. For this reason the review of laboratory data and of the x-ray findings were limited to the thirty-eight patients observed at Presbyterian Hospital. The impressive feature of this review was that no one test was uniformly abnormal; indeed very few were abnormal consistently enough to be of help diagnostically. These few are set forth in Table II, along with an indication of the percentage of instances in which the abnormal results were observed. In this table the figures in parentheses which follow a specific test indicate the number of patients in the series in whom that particular determination was made. Where no parentheses occur, data were available on all thirty-eight patients.

The diminished tolerance for carbohydrates is well known, and was encountered with a high degree of consistency. A much smaller percentage exhibited frank diabetes, and the overall average fasting blood sugar on the entire group was normal. The mildness of the carbohydrate disturbance seen here is compatible with the fact that no instance of diabetic acidosis was met with in this group, and in the 189 reports of

Cushing's syndrome which we reviewed only one such occurrence was recorded.[4]

Although x-ray evidence of demineralization was present in a smaller percentage of the patients than was the abnormal glucose tolerance curve, it was a finding of greater value diagnostically, since the disease involves chiefly those in the younger age group where other causes of demineralization are relatively rare. The most frequent site in which the lack of calcium was demonstrated was the spine, in 74 per cent of the patients, while the skull was involved somewhat less commonly. In a little over half of the patients with demineralization of the spine, compression fractures were present and a small number had spontaneous rib fractures. Unfortunately these bony changes are not confined to the spontaneously occurring forms of hyperadrenalism, as was initially thought. Demartini, Grokoest and Ragan[5] have recently reported the appearance of such fractures in a group of patients on long-term cortisone therapy. Some comfort may be derived from the fact that such lesions have not been seen in patients receiving cortisone in the doses commonly employed for rheumatoid arthritis unless the patient was post-menopausal or bedridden.

An increase in the excretion of so-called "corticoid" material in the urine was anticipated since cortisone and related steroids, the precursors of such urinary products, are thought to be present in excess in Cushing's syndrome. These determinations have been made on ten patients in the present series at a time when they were hyperadrenal. Two different methods have been employed, both based on chemical techniques. In the majority of instances these substances were found to be present in greater than the normal amounts, but I should like to emphasize that this was not true in every case. Among the three patients who excreted normal amounts of these "corticoids" was one with a proven benign adenoma of the adrenal cortex accompanied by all other evidences of the syndrome. Why the excretion of these substances is normal in some cases is not known. However, the current methods of determining these "corticoids" are relatively crude and the values so obtained represent only a fraction of the total excretion. Hence it may be naive to expect the universal finding of an increased urinary excretion of these substances with the present techniques.

The excretion of 17-ketosteroids was normal on the average in this group of patients with Cushing's syndrome. The results are set forth in

TABLE III—17-KETOSTEROID EXCRETION IN CUSHING'S SYNDROME
(mg/24 hr.)

			Average
Adrenal cortical hyperplasia			16.4
	Average	Range	
females (9)	15.5	(7.2-20.9)	
males (5)	18.1	(16.0-27.6)	
Benign adrenal cortical adenoma			5.0
females (7)		(0-8.5)	
Adrenal cortical carcinoma			35.5
male (1)			35.5

Table III, where the patients are grouped according to their underlying adrenal pathology. Our findings are in keeping with the recent report of Forbes and Albright.[6] These authors pointed out that the output of these substances was significantly higher in patients with hyperplastic adrenals than in those in which the adrenal was the site of a benign adenoma. In the latter group it is presumed that the tumor suppresses endogenous ACTH production with atrophy of all adrenal tissue apart from the tumor itself, and if the chief products of the tumor are cortisone-like in character these should contribute but little to the total amount of 17-ketosteroids excreted. As an aside I should like to comment on the fact that all seven of our patients with a benign adenoma were women, a point which Dr. Forbes remarked upon in her report. This, I believe, was due to chance since two reports of a benign adrenal cortical adenoma occurring in males with the features of Cushing's syndrome were encountered in the literature, Lightwood's[7] case of an 18-week-old infant, and Josephson's[8] account of a 17-year-old boy. Dr. Forbes has reported that the values met with in adrenal carcinoma where the excreted steroids may vary widely in character may range from extremely low to extraordinarily high figures, and levels from 1.1 to 649 mg. in twenty-four hours have been recorded. In our one patient with carcinoma in whom this assay was made the values were definitely, but not greatly, elevated.

Although the higher values in patients with hyperplasia than in those with benign tumors is statistically impressive, the level in a given case

TABLE IV—THE EFFECT OF CORTISONE ON URINARY 17-KETOSTEROID EXCRETION IN PATIENTS WITH CUSHING'S SYNDROME

	A.G.† F	*J.J.*† M	*C.C.*† F	*S.K.*† M	*C.R.*‡ M
Control	23.8		14.3	22.1	51.6
	15.1	29.9			40.8
	22.9	25.9	9.0	16.6	39.3
Cortisone 100-200 mg. o.d.	11.2		6.3	13.8	53.1
	8.0		5.8	14.2	56.1
	11.0	22.9	3.6	12.6	63.0
	13.5	23.6		13.1	59.3
		19.2			

† Bilateral adrenal hyperplasia
‡ Adrenal carcinoma

cannot be relied upon to differentiate conclusively between the two conditions because of the known instances in which the values have overlapped. In the last few months, Dr. Jailer has introduced a new diagnostic approach based upon the 17-ketosteroid excretion which shows real promise as a physiological means of distinguishing the patient with a tumor from the one with hyperplasia. He has been kind enough to let me present to you his preliminary results. In his lecture last Friday evening Dr. Jailer pointed out that cortisone, in addition to its real therapeutic benefit in the adrenogenital syndrome, had proven most useful in distinguishing those patients with adrenal tumors from those with hyperplasia. The tumor, being autonomous, was unaffected by the suppression of ACTH induced by the administered cortisone, whereas hyperplastic glands which remained under pituitary influence, showed a diminished output of 17-ketosteroids in response to the cortisone injections. It is also well known that the normal individual like the adrenogenital patient with hyperplastic adrenal cortices, will respond to large doses of cortisone with a reduction in 17-ketosteroid excretion.[9] It was reasoned that the patient with Cushing's syndrome with hyperplastic adrenals might respond similarly, whereas if an adrenal tumor were present providing a constant output of androgenic material, or if a pituitary tumor were present providing a constant supply of ACTH no change in the urinary excretion of the 17-ketosteroids would be expected. To date five patients have been available to assay the validity

TABLE V—ADDITIONAL LABORATORY DATA ON PATIENTS WITH CUSHING'S SYNDROME
(Columbia series, 38 cases)

	Average	*Range*
Red blood cell count million/mm³ (36)	4.62	(3.4-6.9)
White blood cell count /mm³	10,200	(5,800-15,000)
Eosinophiles /mm³	53	
Serum sodium mEq/L (19)	142.6	(136.0-147.0)
Serum potassium mEq/L (16)	3.9	(2.1-5.3)
Serum carbon dioxide content mEq/L (32)	29.6	(21.2-46.2)
Serum chlorides mEq/L (32)	100.3	(78.1-110.2)
Serum calcium mg% (31)	10.0	(9.0-11.3)
Serum phosphorus mg% (27)	3.0	(2.2-4.4)
Basal metabolic rate per cent (34)	—6	(—37 to +32)
Serum cholesterol mg% (32)	263	(138-460)
Radioactive iodine uptake % in 24 hr. (6)	23	(8-51)

of this assumption, and the results are shown in Table IV. The first four patients all have had adrenal cortical hyperplasia established at operation. C.C. and S.K. had each had a course of pituitary radiation totalling 3350 R and 4500 R tumor doses respectively, given twelve and seven months prior to the administration of cortisone. In the first three patients significant falls in the 17-ketosteroid excretion occurred during the four to five days of cortisone administration; in the fourth the fall was less impressive. However, in the patient with an adrenal carcinoma with metastases it is evident that no fall whatever ensued. This patient subsequently underwent total hypophysectomy which had no effect upon the level of androgen excretion, offering further evidence of the autonomous nature of the neoplastic tissue in this instance. Unfortunately, no patients with benign tumors have been available for this type of study as yet. If subsequent experience is as definitive as these few cases would suggest, this approach may provide a useful diagnostic tool in determining the basis of the Cushing's syndrome.

Apart from the studies already mentioned considerable additional laboratory data were available from the present series. For the most part these values approximated normal and they are summarized in Table V. The polycythemia which has long been associated with the syndrome was present in only an occasional patient in our series, the overall average erythrocyte count being high normal. Similarly the white blood

count was at the upper limits of normal on the average, although a few patients showed a significant leukocytosis. Eosinophils were consistently reduced, but as this may be seen in so wide a variety of conditions its diagnostic value is limited. With respect to electrolytes, the present group of patients had normal serum values on the average, and only a rare individual demonstrated the low potassium and low chlorides associated with an elevated carbon dioxide content and sodium which has been associated in the literature with the syndrome. The consistently normal levels of calcium and of phosphorus in the face of marked demineralization is a well recognized feature of the syndrome. Measurements of thyroid function afford a wide range of figures, with little consistent correlation demonstrable in individual patients between the basal metabolic rate, serum cholesterol and radioactive iodine uptake values.

I have already mentioned the help derived from x-ray in establishing the diagnosis of Cushing's syndrome. In addition to providing evidence of osteoporosis, specific data have been obtained from x-ray as to the presence or absence of adrenal tumors. The larger tumors may occasionally be suspected from distortion of the renal outlines on a simple flat plate; one such case was encountered in the present group. Of the nine patients proven to have tumors, six had intravenous pyelograms; in only half of these was the presence of tumor indicated. This is not surprising since the majority of the benign adenomas of the adrenal are relatively small, and would not be expected to disturb the normal spacial relationships in the adrenal area. For this reason, the technique of peri-renal air insufflation was introduced to aid in delineation of the retroperitoneal space. In all, twenty-nine patients in the present group had such airograms performed, and as Cahill[10] mentioned several years ago, the interpretation of these films in patients with Cushing's syndrome is rendered particularly difficult by virtue of the "edema in the perirenal tissue" in this condition. The record bears this out. In twenty-three of the twenty-nine patients the airogram was considered suspiciously abnormal; of the sixteen who were subsequently explored and an additional two from whom autopsy data were available, a tumor was found in only eight. However, it should be added that no falsely negative results were encountered. It is possible that the newer technique of introducing air presacrally may offer better delineation, but we have not had sufficient experience with this to be certain at the present time.

Treatment

The treatment of Cushing's syndrome should logically be directed at reducing the output of adrenal hormones. The method selected will vary with whether the physician directing the therapy belongs to the school which believes the pathology lies primarily in the pituitary, or in the adrenal or even in the hypothalamus. The available evidence as to the site of origin of this condition is confusing. In briefest summary it is as follows: Cushing in his original paper[2] attributed the disease to the presence of a basophilic adenoma in the pituitary. However, the many cases now on record in which serial sections of the anterior hypophysis have failed to reveal such a lesion make this hypothesis untenable. Others have thought that the disease arises in the adrenals. Cases secondary to adrenal carcinoma would be compatible with this theory but what explanation can be offered for cases in which no abnormality in the size or histological structure of the adrenal has been demonstrated? In 1935 Crooke[11] described a characteristic hyaline change in the pituitary basophile cells in cases with Cushing's syndrome. Extensive study, among which should be mentioned the work of Thompson and Eisenhardt,[12] has confirmed the almost universal finding of this abnormality in such patients. It has, however, been seen in patients with virilism as well as in the classical Cushing's syndrome,[13] and recent work of Laqueur[14] suggests that the hyaline change may be secondary to excess circulating adrenal hormones, rather than the primary cause of adrenal secretion. Her evidence rests on the demonstration of similar changes in the pituitaries of patients who at the time of death were under treatment with exogenous ACTH or cortisone. In 1944 Heinbecker[15] proposed the theory that the initial lesion in the syndrome lay in the hypothalamus where he consistently found abnormalities. However, it seems likely that these hypothalamic lesions, in turn, are secondary rather than of primary importance since Castor et al.[16] have reported the experimental production of lesions in similar areas with ACTH and cortisone. Considering these many conflicting findings, Dr. Plotz, Dr. Ragan and I thought it would be of interest to summarize the present clinical material with respect to the frequency and variety of pathology encountered in the adrenal and pituitary glands in Cushing's syndrome. In ninety-eight patients there were sufficient data available on the condition of both of these glands. It was somewhat difficult to analyze the material

TABLE VI—RELATION BETWEEN PITUITARY AND ADRENAL LESIONS
(97 Autopsied Cases — Cushing's Syndrome)

Pituitary Findings	*Adrenal Findings*						*Total*
	Hyperplasia of adrenals	*Carcinoma of adrenals*	*Unilateral* benign tumor with atrophy of opposite gland*	*Hemorrhage or infarcts in one or both adrenals*	*Hypoplasia of adrenals*	*Normal adrenals*	
Crooke's hyalinization without other pituitary abnormality	17	11	5			1	34
Basophilic adenoma	24		1	2	1	3	31
Increased number basophils or basophilic invasion of posterior lobe	4	1	1			2	8
Mixed basophilic-chromophobe adenoma	3						3
Chromophobe adenoma	5	1				1	7
Mixed chromophobe-eosinophilic adenoma	1						1
Eosinophilic adenoma	1	1					2
Increased number eosinophils		1					1
Unspecified adenoma	1		1			1	3
Atrophy and fibrosis	1						1
Scar destroying neurohypophysis and pars intermedia						1	1
Normal	1	2	3				6
Total	58	17	11	2	1	9	98

* Includes two cases with unilateral hypertrophy of one adrenal without actual tumor.

since it represented the work of many different pathologists who used descriptive terminology which varied considerably. Also the data perforce included cases recorded prior to the publication of Crooke's paper, hence the percentage in which the Crooke's change was reported is undoubtedly falsely low. Its high incidence can only be guessed at from the fact that in all the cases where this hyaline change was searched for, only four authors specifically denied its presence. The results of the analysis are set forth in Table VI. The several categories of adrenal findings are listed horizontally, and the various pituitary lesions are set forth vertically. "Hyperplasia" of the adrenals was arbitrarily defined

as a combined adrenal weight of greater than 15 grams and/or histological evidence of overactivity. The truly impressive feature about this chart is the extraordinary variety of adrenal and pituitary pathology which has been reported in the Cushing's syndrome. We encountered twenty-nine different possible combinations of lesions, all of which have been associated with the same clinical picture. The combination most commonly met with was hyperplasia of the adrenals with a basophilic adenoma of the pituitary. The second most frequent was hyperplasia of the adrenals, with no pituitary abnormality apart from the ubiquitous change in the basophils and, due to the inevitable omission from this group of cases antedating the description of Crooke's change, this particular category may well be the one most commonly encountered. Third most common was a malignant tumor of the adrenal with hyaline changes in the pituitary basophils. Two additional points should be emphasized. Of the various adrenal abnormalities hyperplasia is the one most often encountered while the benign adrenal adenoma occurs in only a small percentage of the cases. Of the pituitary lesions, basophilic adenomas were found in only one-third of the patients; however, pituitary tumors of one sort or another occurred in half of the patients.

From these data it is evident that no blanket outline for treatment can be made but that the approach to therapy must vary with the underlying pathology present in the individual patient. In every work-up there should be investigation to rule in or out the presence of a pituitary tumor. It is extremely rare for the basophilic adenoma to give local symptoms or signs, i.e., restriction of the visual fields or enlargement of the sella, but since a significant percentage of the pituitary tumors in this group of patients may be mixed cell type, chromophobic, or even eosinophilic, signs of local expansion should be searched for and, if found, treatment would logically be directed initially to the pituitary.

In the absence of symptoms suggesting a pituitary neoplasm an effort should be made to rule out an adrenal tumor. When more patients have been studied this may be satisfactorily settled physiologically by the administration of cortisone as described above. However, at the present, direct visualization affords the only decisive means of arriving at this knowledge. Because the removal of such a tumor may be followed by complete remission of the syndrome early exploration of the adrenal area has seemed justified despite the small percentage of those with Cushing's disease showing such tumors. In our group, twenty-two patients

TABLE VII—ADRENAL OPERATIONS IN CUSHING'S SYNDROME

	Total	*Unchanged*	*Sl. imp.*	*Cured*	*Died*
Removal benign adrenal adenoma	6			3	3
Exploration of one adrenal	2	1			1
Biopsy and/or partial resection of one or both adrenals for hyperplasia	10	10			
Subtotal adrenalectomy for hyperplasia	2		2		
Removal adrenal carcinoma	2		1*		2

* Improvement 11 months

were subjected to exploration of one or both adrenals (Table VII). Of the six patients with benign cortical adenoma, three died in the immediate postoperative period and three went on to complete remission of their disease. The three who died were all operated on prior to the availability of ACTH or cortisone. The three who survived all had somewhat stormy postoperative courses. It is interesting that one of these patients, as the evidences of hyperadrenalism cleared, developed disabling arthralgias which persisted for several months. The fatal outcome in one patient who died after exploration without removal of any adrenal tissue was due to the development of a hemolytic streptococcal wound infection with necrosis and gangrene of the abdominal wall, and ultimately generalized peritonitis. This progressed despite wide incision and drainage and the use of sulfadiazine. In the ten patients with hyperplasia of the adrenals in whom biopsy or partial resection of one or both glands was performed, the operation produced no significant change in their course. One of these patients, we have heard, subsequently underwent a subtotal adrenalectomy at the Mayo Clinic with marked improvement. In the two patients in the Presbyterian Hospital series subjected to bilateral subtotal adrenalectomy, the initial results have been somewhat encouraging, though not dramatic. In one patient there has been some improvement in carbohydrate tolerance and in the severe facial acne, decrease in edema and some clearing of his paranoid psychosis. Of the two individuals with adrenal carcinoma, one was unimproved and died four months after his initial operation with widespread metastases; the other enjoyed a remission of eleven months before return of her symptoms and subsequent death from metastases.

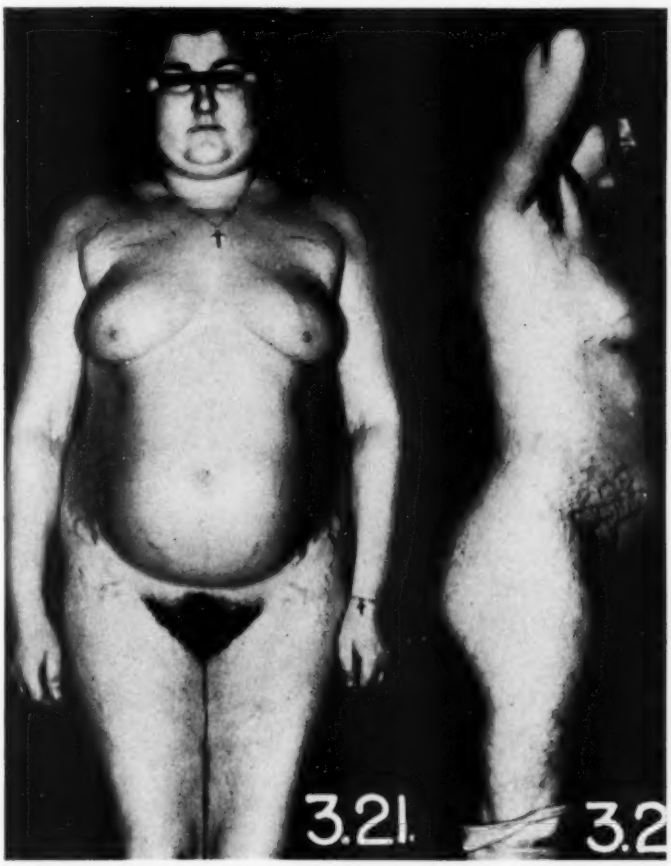


*Figure 1—M.F. Cushing's syndrome, prior to therapy, 3/21/39.

The number of patients in the present group who have had pituitary irradiation now totals twenty. The results obtained by us have paralleled those recently reported by Sosman.[17] Ten of the present twenty patients enjoyed some degree of remission following x-ray, although in only half this number has the improvement been maintained to date. The dosages employed and the duration of time over which therapy was given have varied widely, and no correlation was evident between these

* Figures 1-4, photographs reproduced with the permission of Presbyterian Hospital, New York, N. Y.

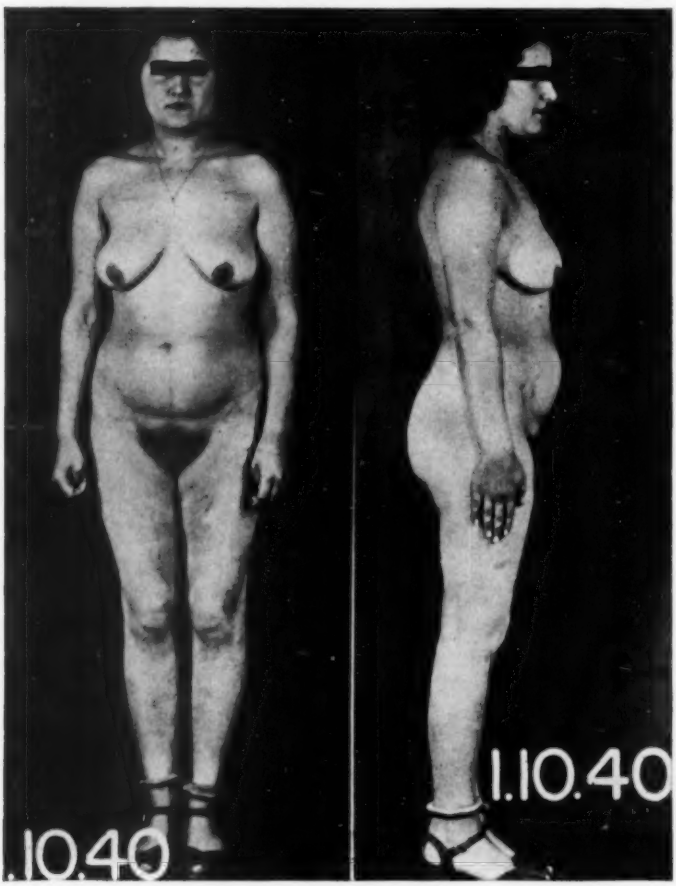


Figure 2—M.F. Cushing's syndrome, 9 months after pituitary irradiation.

factors and the degree of improvement. The accompanying figures show how dramatic this improvement can be. The first photograph shows the patient M.F. as she appeared in 1939 at the age of seventeen, at which time she was suffering from the classical symptoms and signs of Cushing's syndrome, of which the obesity, facial fullness and striae are visible here. In March of 1939 she received a tumor dose totalling only 800 R over a twenty-eight-day period. No other treatment was given. The

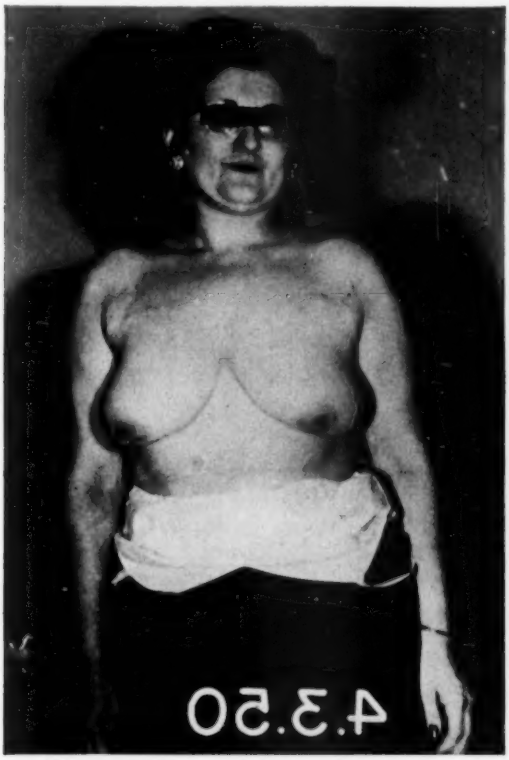


Figure 3—M.F. Cushing's syndrome, 11 years after pituitary irradiation.

next photograph shows her as she appeared in 1940, nine months later, by which time there has been a striking change in her appearance, and the third picture, taken in 1950, twelve years after the onset of her disease, indicates that the remission still persisted.

In the group of patients treated at Presbyterian Hospital only two were treated with androgens in large doses over a prolonged period of time. The results are difficult to interpret because both patients received pituitary and/or adrenal irradiation shortly before or after androgen therapy. Hence our experience with this type of therapy does not permit any conclusions.

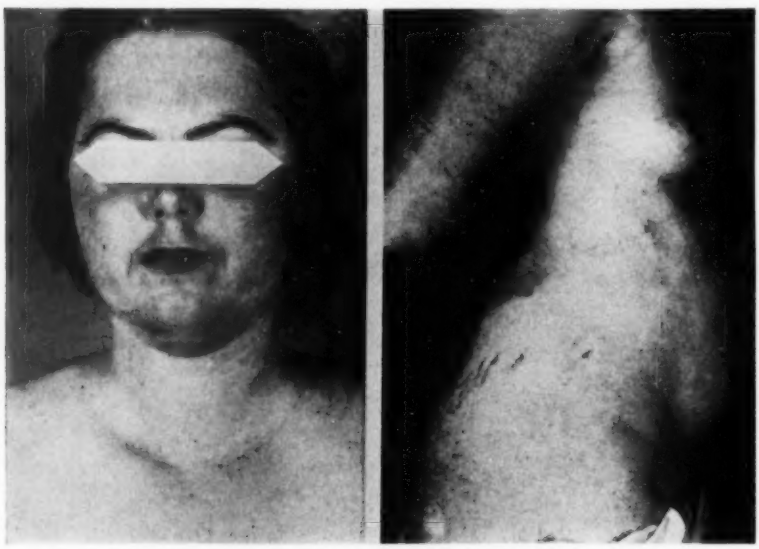


Figure 4—R.C. Cushing's syndrome, 1949.

Before leaving the discussion of treatment, I should like to show one additional figure. The fourth photograph was taken in 1949 when the patient was twenty-nine, having had evidences of the disease for two years. The abnormal features are striking. Bilateral partial resection of both adrenals was performed in June and July of that year. In August she developed an acute psychosis and was admitted to the hospital during which time pituitary irradiation totalling a tumor dose of 1400 R was administered in the course of sixteen days. Her symptoms and her psychosis persisted unabated for the next year during which time she was hospitalized in a state psychiatric hospital, given a course of electric shock therapy with "improvement at first, then later relapse." Beginning in the Fall of 1950 with no further therapy there occurred a gradual spontaneous improvement in her condition—clearing of her hirsutism and skin rash, resumption of menses, clearing of her mental picture and disappearance of her severe hypertension, such that multiple faded striae are at present the only reminder of the previous existence of her Cushing's disease. I mention this case only to emphasize that spontaneous re-

TABLE VIII—CAUSES OF DEATH IN CUSHING'S SYNDROME BASED ON 115 AUTOPSIED REPORTS

(Multiple causes listed in 37 cases)

Infection	54 (6 due to tbc.)
Cardiac failure	31
Cerebrovascular accident	8
Uremia	6
Postoperative death	23 (8 adrenal insufficiency)
Carcinoma of adrenal	7 (present in 11 others)
Tumor of thymus	6
Carcinoma of pancreas	4
Sympathicoblastoma	1
Pulmonary infarction	4
Asthenia	2
Acute gastrointestinal hemorrhage	2
Suicide	2
Renal colic	1
Not listed	4

missions can occur in this syndrome and that interpretation of the results of treatment must take this into consideration.

This happy occurrence is unfortunately all too rare, and one of the most impressive features of this survey was the overall mortality figure. Eighteen of the thirty-eight patients comprising the present series were dead at the end of five years. There are instances in which the disease runs a more benign course, of which the most famous example, probably, was Cushing's first patient, Minnie G. This woman, at the time she was originally reported, had had symptoms of her disease for twenty-nine years. However, the severity of Cushing's syndrome is worth emphasizing as a matter to be taken into serious consideration before undertaking long-term treatment with ACTH or cortisone in patients suffering from non-fatal diseases. From the eight autopsied cases in the present series and from an additional 107 autopsy reports available from the literature, Table VIII has been compiled, listing the more frequent causes of death among patients with Cushing's syndrome. The results are those that might have been predicted from a consideration of the symptoms of the disease. The leading cause of death was infection. Since many of the cases antedated the introduction of antibiotics this is less impressive a figure than it initially appears. However, it does serve to emphasize that the

decreased resistance of hyperadrenal individuals to infection and among these tuberculosis, as well as the pyogenic organisms, must be kept in mind. In confirmation of this there stands recent experimental work indicating the increased susceptibility of hyperadrenal animals to tuberculosis and to a variety of organisms.

The second major cause of death in these predominantly young individuals was cardiovascular disease—cardiac failure, cerebrovascular accidents and uremia. This undoubtedly was related to the severe degree of hypertension so consistently present, and possibly to the widespread presence of arteriosclerosis in these patients. Arteriosclerosis was noted as present in the autopsy reports of fifty-one of the fifty-eight cases in which data on this point were available. Since arteriosclerosis is so common a finding in adult autopsy material, too much emphasis cannot be placed on this finding. However, conclusive evidence of the increased incidence of such lesions under cortisone therapy has appeared recently in a report by Etheridge and Hoch-Ligeti[18] based on autopsy material from children, where arteriosclerosis normally is at a minimum. Comparing the aortas of cortisone-treated patients under eleven years of age with those of a control group, these authors found an increased deposition of lipid in the steroid injected group.

Postoperative deaths accounted for exitus in a distressingly large number of patients. A certain fraction of these could be ascribed to adrenal insufficiency following the removal of a functioning tumor; the rest were due to unexpected postoperative infections such as in the patient I described above. Carcinoma of the adrenal was listed as the cause of death in only a small percentage, the majority of patients with adrenal carcinoma dying of immediate causes other than the neoplasm.

In the Presbyterian Hospital series there were no patients in whom neoplasms were found in areas other than the pituitary or adrenal. In this respect, the present group is at variance with data available in the literature, from which the patients comprising the ensuing three groups are drawn.

In six patients thymic tumors were reported; in four of these the tumors were of malignant nature. Another four patients had carcinoma of the pancreas, while still another died with a sympathicoblastoma. These patients raise the question as to whether these neoplasms in some fashion acted as initiating agents for the hyperadrenalism, or vice versa, or whether the presence of over-activity of the adrenals was in some

manner carcinogenic. It is interesting to note that both the thymus and pancreas are tissues which may be affected in the course of Cushing's syndrome. The thymus commonly shows marked atrophy; the pancreas, though histological changes are less common, may be under physiological stress from the disturbed carbohydrate function. In addition to tumors there were several reports of abscesses and fatty necrosis involving the pancreas. From the reported cases it is impossible to answer the question as to whether the neoplasms ante- or post-dated the appearance of Cushing's syndrome. In only one instance was an attempt made to remove the neoplasm, in the patient reported by Hubble.[19] In this instance the operation was followed by death within twenty-four hours, far too soon to state the effect of the removal of the tumor upon the hyperadrenalism.

Four patients died of pulmonary infarctions. In addition, pulmonary or myocardial infarctions were noted in seventeen of twenty-seven cases in which these data are available. In one case death was listed as due to renal colic. In connection with this it is of interest to note that four patients in the present series have had renal calculi, which may well be related to the disturbed calcium metabolism. It is tempting to speculate that the two deaths ascribed to asthenia might have been due to low potassium levels; however, there was not sufficient information to draw this conclusion. Finally, the two suicides are not surprising in view of the frequency with which severe emotional disturbances have been encountered.

Summary

In summary, this review of the natural history of Cushing's syndrome has confirmed many well recognized features of the disease and has served to emphasize the following:

1. The impressively high incidence of hypertension (92 per cent), abnormal mental reactions (66 per cent) and of unusual infections or poor wound healing (42 per cent).

2. The frequency with which diminished carbohydrate tolerance (94 per cent), demineralization of the spine (74 per cent) and increased urinary excretion of the so-called corticoids (70 per cent) were met with, while the remainder of laboratory studies were but rarely abnormal.

3. The grave prognosis of the disease, with a mortality of 50 per cent by the end of five years and the frequency of the occurrence of

infections and cardiovascular complications among the listed causes of death.

4. The extraordinary variety of adrenal and pituitary pathology which has been associated with the clinical picture of Cushing's syndrome. In ninety-eight patients, basophilic adenomata were reported in 31 per cent although in a total of 50 per cent some type of pituitary tumor was present. Benign adrenal tumors were noted in 11 per cent, malignant tumors in 17 per cent.

Among the thirty-eight patients studied at the Columbia-Presbyterian Medical Center treatment has included:

a) Removal of a benign adrenal adenoma with a complete remission in the three patients who survived the stormy immediate postoperative period;

b) Removal of an adrenal carcinoma which was followed by death from metastases in two patients, one of whom enjoyed a year's remission;

c) Subtotal bilateral adrenalectomy with resultant slight improvement in two patients;

d) Pituitary irradiation which has been followed by temporary improvement in ten of twenty patients. This improvement was maintained in five instances.

A spontaneous and complete remission was seen in one patient.

REFERENCES

1. Plotz, C. M., Knowlton, A. I. and Ragan, C. The natural history of Cushing's syndrome, *Amer. J. Med. 13*:597-614, 1952.
2. Cushing, H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism), *Bull. Johns Hopkins Hosp. 50*:137-95, 1932.
3. Perera, G. A. Cortisone and blood pressure, *Proc. Soc. exp. Biol. Med. 76*:583-85, 1951.
4. Petresco, M., Sutianu, A. and Olaru, Z. Syndrome de Cushing; considérations sur sa pathogénie, *Bull. Acad. Med. Roum. 2*:592-603, 1937.
5. Demartini, F., Grokoest, A. W. and Ragan, C. Pathological fractures in patients with rheumatoid arthritis treated with cortisone, *J. Amer. med. Assoc. 149*:750-52, 1952.
6. Forbes, A. P. and Albright, F. A comparison of the 17-ketosteroid excretion in Cushing's syndrome associated with adrenal tumor and with adrenal hyperplasia, *J. clin. Endocrin. 11*:926-35, 1951.
7. Lightwood, R. C. Tumour of the suprarenal cortex in an infant of 18 weeks, *Arch. Dis. Childh. 7*:35-42, 1932.
8. Josephson, B. The adrenal cortical syndrome in a case with tumor from an accessory adrenal gland, *Acta med. scand. 90*:385-96, 1936.
9. Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. F. Observations on the physiologic effects of cortisone and ACTH in man, *Arch. intern. Med. 85*:199-258, 1950.

10. Cahill, G. F., Melicow, M. M. and Darby, H. H. Adrenal cortical tumors; the types of nonhormonal and hormonal tumors, *Surg. Gynec. Obstet. 74*:281-85, 1942.
11. Crooke, A. C. A change in the basophil cells of the pituitary gland common to conditions which exhibit the syndrome attributed to basophilic adenoma, *J. Path. Bact. 41*:339-49, 1935.
12. Thompson, K. W. and Eisenhardt, L. Further consideration of the Cushing syndrome, *J. clin. Endocrin. 3*:445-52, 1943.
13. Mellgren, J. The anterior pituitary in hyperfunction of the adrenal cortex; anatomical study with special reference to syndroma Morgagni and notes on prostatic hypertrophy, *Acta path. microbiol. scand. Supp. 60*:1-177, 1945.
14. Laqueur, G. L. The human hypophysis in diseases of the adrenal cortex, *Stanford med. Bull. 9*:75-87, 1951.
15. Heinbecker, P. Pathogenesis of Cushing's syndrome, *Medicine 23*:225-47, 1944.
16. Castor, C. W., Baker, B. L., Ingle, D. J. and Li, C. H. Effect of treatment with ACTH or cortisone on anatomy of the brain, *Proc. Soc. exp. Biol. Med. 76*:353-57, 1951.
17. Sosman, M. C. Cushing's disease—pituitary basophilism; Caldwell lecture, 1947, *Amer. J. Roentgenol. 62*:1-32, 1949.
18. Etheridge, E. M. and Hoch-Ligeti, C. Lipid deposition in aortas in younger age groups following cortisone and adrenocorticotropic hormone. *Amer. J. Path. 28*:315-19, 1952.
19. Hubble, D. Cushing's syndrome and thymic carcinoma, *Quart. J. Med. 18*: 133-47, 1949.

THE TWENTY-SIXTH ANNUAL GRADUATE FORTNIGHT

THE NEW YORK ACADEMY OF MEDICINE

October 19 to 30, 1953

DISORDERS OF THE BLOOD AND THE BLOOD-FORMING ORGANS

Evening Lectures — Afternoon Hospital Clinics

Morning Panel Discussions — Scientific Exhibit

Complete program to be announced later

For registration, address the Secretary

GRADUATE FORTNIGHT

THE NEW YORK ACADEMY OF MEDICINE

2 East 103 Street, New York 29, N. Y.

METABOLIC EFFECTS OF INSULIN*

DeWitt Stetten, Jr.

Chief, Division of Nutrition and Physiology,
The Public Health Research Institute of the City of New York, Inc.

Since its discovery some thirty years ago insulin has been subjected to investigation by most of the techniques available to the chemist and the biologist. The magnitude of the resultant literature is indicated by the fact that in a very incomplete survey made recently in excess of 8000 titles appear. The reasons for the biologist's interest in insulin will be apparent to this audience. The chemist has been attracted to insulin as a model well suited for study because it is a protein of high purity which has been available in the crystalline state for the past several years. It is, for a protein, a compound of unusual stability and will readily withstand treatment that would denature many other proteins. It has a relatively low molecular weight and therefore has offered promise in studies designed to elucidate its structure. On hydrolysis it yields a mixture of amino acids uncontaminated by sugars, porphyrins or any other structural units, and it may therefore be listed as a "simple" protein.

Because of these and other attractive characteristics, solutions of insulin have been subjected to gravitational fields in the ultracentrifuge, to electrical fields in the electrophoresis apparatus. The capacity of insulin to scatter light in solution and to diffract x-rays in each of its two crystalline forms has been recorded. The curious property of insulin to enter reversibly into the formation of insoluble, physiologically inert "fibrils" has been studied, and the participation of various divalent cations, notably zinc, in its crystal, has been explored. Insulin has been subjected to attack by a host of chemical reagents and it has even been exposed to neutron bombardment in the atomic pile.

The analytical chemist has successfully applied the tools of his trade to insulin and excellent analyses for each of its constituent amino acids have been carried out. Of unusual interest and importance have been the studies of Sanger[1] who has presented evidence that, upon oxidative

* Presented at the 25th Graduate Fortnight of The New York Academy of Medicine, October 13, 1952. From the Division of Nutrition and Physiology, The Public Health Research Institute of the City of New York, Inc., New York.

TABLE I—COMPOSITION OF THE A AND B CHAINS AND OF BEEF INSULIN
AMINO ACID COMPOSITION OF A AND B CHAINS OF INSULIN

(residues per molecule)

Amino Acid	*A*	*B*	*2(A+B)*
Glycine	1	3	8
Alanine	1	2	6
Valine	2	3	10
Leucine	2	4	12
Isoleucine	1	0	2
Proline	0	1	2
Phenylalanine	0	3	6
Tyrosine	2	2	8
Glutamic Acid	4	3	14
Aspartic Acid	2	1	6
Serine	2	1	6
Threonine	0	1	2
Cystine/2	4	2	12
Arginine	0	1	2
Histidine	0	2	4
Lysine	0	1	2
Amide	4	2	12
Molecular Weight	3,400	2,300	11,500

rupture of disulfide bridges, the insulin molecule gives rise to two and only two kinds of polypeptide fragments. Combining this information with that derived from other studies mentioned above, most investigators generally agree today that the monomeric insulin molecule has a molecular weight of about 12,000, although it may exist in micelles of three and four times this size. This unit of 12,000 comprises four polypeptide chains linked to each other by disulfide bridges extending between cysteine residues in adjacent chains. These four chains appear to be of only two species, named A and B respectively, and two of each of these are combined to form one insulin molecule. In Table I are given the results of the most recent analytical studies in which the composition of each type of chain, as well as that of the intact beef insulin molecule, is tabulated. It will be seen that most of the common amino acids are represented, with the notable exceptions of tryptophan and methionine. When compared with other proteins, insulin is rich in valine, leucine and glutamic acid, and exceptionally rich in cystine. In the native insulin molecule, all of the sulfur is in the oxidized–cystine–condition. Certain differences in amino acid composition of the A chain have been reported when pig, sheep and beef insulins are compared[2] but in contrast to hemoglobins or serum albumins, insulins derived from different

PHE-VAL-ASP-GLU-HIS-LEU-CYS-GLY-
SER-HIS-LEU-VAL-GLU-ALA-LEU-TYR-
LEU-VAL-CYS-GLY-GLU-ARG-GLY-PHE-
PHE-TYR-THR-PRO-LYS-ALA.

Figure 1. The Sequence of Amino Acids in the B Chain of Insulin (after Sanger and Tuppy,[3] *Biochem. J.* 49:481-90, 1949. Reprinted by permission of the Cambridge University Press, publishers of the *Biochemical Journal*).

GLY-ISOLEU-VAL-GLU-GLU-CYS-
CYS-ALA-SER-VAL-CYS-SER-LEU-
TYR-GLU-LEU-GLU-ASP-TYR-CYS-
ASP.

Fig. 2. The Sequence of Amino Acids in the A Chain of Insulin (after Sanger and Thompson,[4] *Biochem. J.* 52:iii, 1952. Reprinted by permission of the Cambridge University Press, publishers of the *Biochemical Journal*).

species are, so far as they have been studied, very similar in physical and in physiological properties.

Sanger has carried his study of insulin structure a great step beyond the mere collection of analytical information. He has devised a reagent, dinitrofluorobenzene, which not only binds specifically to primary amino groups under mild conditions but also conveniently imparts a yellow color to any compound with which it reacts. Combining the use of this reagent with techniques of partial hydrolysis, separation of fragments by chromatography and ultimate identification of some sixty lower peptides thus prepared, Sanger and Tuppy[3] have shown that their accumulated evidence fits uniquely the sequence of amino acids in the B chain shown in Figure 1. Similar studies of the A chain have very recently been reported[4] and in Figure 2 is given the amino acid sequence of this polypeptide. When such details as the arrangement of the disulfide bridges between chains and the location of the amide residues are known, the chemist will finally have realized a long-standing ambition, he will be able to write a complete structural formula of a protein.

It would be gratifying if I could report to you that now that we are approaching complete knowledge of the structure of insulin, we are enabled to apply this knowledge toward an explanation of its physiological action. It is somewhat disheartening to have to admit that although insulin is of all proteins the one most intimately known, the knowledge of its structure has to date contributed nothing to the understanding of its effect upon carbohydrate metabolism. The purely physical and chemical assaults on the study of insulin and the biological attack have thus far not established contact.

The proper study on insulin function requires that insulin of highest purity be available. The presence of a physiologically active contaminant in many purportedly pure samples of insulin has been established over the past several years. The contaminant has been characterized as the hyperglycemic-glycogenolytic (or H-G) factor and means of separating it from insulin have been devised. Largely due to the work of Sutherland[5] we now know that the H-G factor arises from the α-cells of the islets of Langerhans. Its essential action is quite similar to that of epinephrine in that it favors the breakdown of liver glycogen to yield blood glucose operating, apparently, on the enzyme phosphorylase much as epinephrine is stated to do. The endocrinological significance of H-G factor in the intact animal is for the present an unknown quantity. It has been suggested that the mildness of the diabetes which follows total pancreatectomy in man is related to the fact that the α-cells, the source of H-G factor, as well as β-cells, the source of insulin, are removed.

It is axiomatic in endocrinology that the hormone must come in contact with the effector organ. In the case of insulin this contact has been the subject of intensive study by Stadie and his collaborators.[6] Convincing evidence has been presented that insulin is very rapidly bound to the surface of such tissues as muscle, adipose tissue and mammary gland. The union between insulin and effector organ is a very firm one which withstands prolonged washing. Of interest are observations which suggest that the binding of insulin by muscle is interfered with by certain anterior pituitary fractions known to be insulin antagonists. Present evidence suggests that the active diabetogenic material of the anterior pituitary is either a contaminant or a biological derivative of growth hormone.

Before introducing the matter of the probable chemical site or sites of action of insulin in the animal body it may be profitable to review briefly certain of the pertinent reactions which occur in the course of glucose metabolism. It is generally held today that, simultaneously with or shortly after its entry into the intracellular compartment of most or all cells, glucose undergoes irreversible phosphorylation by adenosine triphosphate to yield glucose-6-phosphate. The enzyme catalyzing this reaction, hexokinase, more precisely called glucokinase, is ubiquitous in its distribution. This reaction is an obligatory first step in all of the important metabolic fates of glucose in the animal. The glucose-6-phosphate formed in this reaction has several possible fates, indicated in Figure 3:

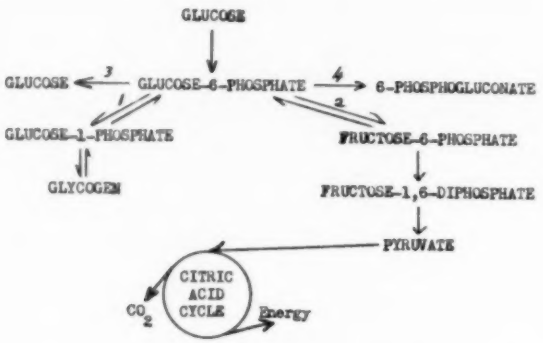


Figure 3

Figure 3. Metabolic Fates of Glucose-6-Phosphate.

1. Transformation to glucose-1-phosphate from which glycogen and other glucosides arise.

2. Rearrangement to fructose-6-phosphate, which, after further phosphorylation to fructose-1,6-diphosphate, may proceed over the steps outlined by Embden, Meyerhof and others to pyruvic and lactic acids. This process serves, in the animal, as the main source of fuel for the all-important citric acid cycle, the major energy-yielding process in the body.

3. Hydrolysis, by an appropriate glucose-6-phosphatase to glucose and inorganic phosphate. This enzyme has been demonstrated in liver and presumably occurs in kidney and intestinal mucosa but is absent from muscle.

4. Oxidation to 6-phosphogluconic acid which serves as precursor for the important pentose, ribose, of nucleic acids and initiates a pathway of oxidation currently referred to as the "hexosemonophosphate shunt."

When insulin is injected into a normal human or an experimental animal, a prompt fall in the level of blood glucose results. The controversies of the past generation in regard to the mechanism of this decline have largely been resolved and it is generally agreed that insulin provokes an increase in the rate of glucose utilization. The synthesis of glycogen from glucose, especially in muscle, is strikingly enhanced. The breakdown of glucose to lactate and pyruvate is accelerated, and the complete oxidation of glucose to CO_2 is also speeded up, as manifested by a rise in respiratory quotient toward unity.

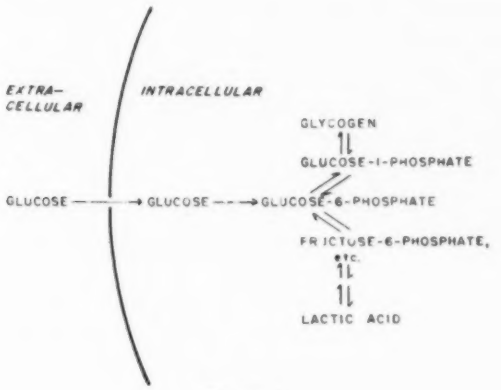


Figure 4

Figure 4. The Entry of Glucose into the Cell and its Phosphorylation.

If, by way of contrast, a severely diabetic patient or an experimental animal deprived of normal insulin supply is studied, the capacity of muscle and liver to utilize glucose is found to be diminished. This is reflected in an elevated blood glucose concentration, a decreased capacity to generate glycogen from glucose and a diminution in rate of lactate production from glucose. The rise in blood lactate as well as the rise in respiratory quotient found after injection of glucose into the normal subject is markedly decreased or absent in the diabetic.

If these several manifestations of excessive or deficient insulin supply are referable to a common or single biochemical mechanism, it would appear that the site of this mechanism would have to lie between glucose and glucose-6-phosphate. The pathways of glucose utilization diverge at glucose-6-phosphate and if a single point of attack is postulated to account for effects on glycogenesis as well as on pyruvate and CO_2 production, that point must be prior to glucose-6-phosphate. It is worth noting in this regard that the diabetic organism, not competent to burn glucose to CO_2, continues to burn glycogen to CO_2 quite normally, a finding which eliminates most of the other reactions in Fig. 3 for consideration.

There are two events which may be pictured as intervening between extracellular glucose and intracellular glucose-6-phosphate (Fig. 4). First, the glucose must cross the cell barrier; second, it must become phosphorylated. Evidence has been presented which implicates each of these steps in the explanation of insulin action.

That insulin in some fashion favors the glucokinase-catalyzed phosphorylation of glucose was first clearly proposed by Cori and collaborators.[7] These workers have found that glucokinase of muscle or brain, in cell-free solution, may be inhibited by a combination of pituitary and adrenocortical materials and that insulin effects a release of glucokinase from this inhibition. Whereas insulin could not be shown to exert any direct action upon glucokinase, the activity of a suitably inhibited preparation of glucokinase could be *indirectly* enhanced by addition of insulin.

The picture of insulin action arising from this concept has many satisfactory features. Not only is insulin operating to favor glucose utilization at the right point, but also the antagonism between insulin on the one hand and pituitary and adrenocortical substances on the other is neatly explained. The picture leaves unexplained the well-known extreme insulin sensitivity of the hypophysectomized or adrenalectomized animal. In addition it has been subject to criticism in several quarters as a result of difficulties experienced by others in attempting to reproduce these and similar hormonal effects in cell-free systems. In fact many workers have come to the conclusion that insulin may exhibit its effects only upon intact cells and that hormonal effects upon enzymes in solution remain to be convincingly demonstrated.

The only remaining locus of action of insulin to be considered is in the transport of extracellular glucose to the intracellular compartment. The view that insulin specifically favors this transport has recently derived vigorous support from the studies of Levine and coworkers.[8, 9] Working with eviscerate dogs, these investigators have measured the volume of water throughout which an intravenously administered dose of galactose is distributed. They have found that this volume is considerably less than the total body water but rapidly increases to equal the total body water if insulin is injected. The finding is of particular interest in view of the fact that galactose apparently undergoes no chemical reactions whatsoever in their eviscerate preparations. The explanation appears to be that insulin renders the previously inaccessible intracellular compartment of muscle readily accessible to galactose. Added weight is given to the argument by the finding that insulin responses were obtained with *D*-xylose *L*-arabinose, which share with galactose the same configuration about carbon atoms 1, 2 and 3 as that of glucose (See Fig. 5). All other sugars tested which differed from this configuration showed no insulin effect.

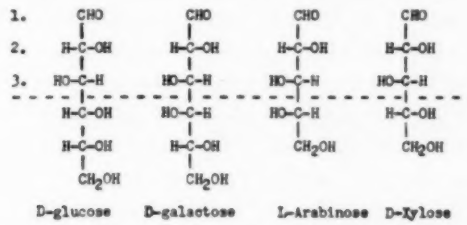


Figure 5. Formulae of the Sugars which Show Insulin Response in the Eviscerate Dog. Note that these sugars have the same configuration at carbon atoms 1, 2 and 3.

Arguing by analogy, it is proposed that insulin in some fashion permits rapid transport of glucose into the intracellular compartment of such tissues as muscle and that this effect is not a consequence of phosphorylation since it may be observed in sugars like galactose, xylose and arabinose which are not phosphorylated in the preparation employed. Glucose itself can not be studied conveniently by this technique in view of its rapid irreversible disappearance after entry into muscle cells.

The picture of insulin action arising from these experiments has many points in its favor. It must be borne in mind that thus far the argument is entirely by analogy based upon experiences with unmetabolized sugars. Whereas at the present time a final statement can not be made, it may be pointed out that the area of disagreement is not wide and we may hope for a resolution of this problem in the near future. Whether it acts upon the transporting or the phosphorylating step, insulin undoubtedly favors the formation of intracellular glucose-6-phosphate from extracellular glucose.

The effects of insulin considered thus far are those relating to glucose and its immediate derivatives. In addition to these compounds, other metabolites, including fats and proteins, are affected when insulin is either deficient or present in excessive amount. It has long been known that the untreated diabetic subject loses weight, that weight gain may be expected after administration of insulin. These changes in weight are reflected in changes in quantity of body fat. Some years ago we studied this effect in experimental animals[10, 11] and were able to show that insulin administration markedly enhances fatty acid synthesis, while in diabetic animals fatty acid synthesis is subnormal. More recently fatty acid synthesis from acetic acid has been studied in various laboratories in vitro using liver slices[12, 13] and it has been shown that the liver of the diabetic animal gen-

erates long-chain fatty acids from acetate more slowly than does the normal liver. The converse finding, acceleration of lipogenesis from acetate upon addition of insulin has also been reported.[14-15]

These effects of insulin deprivation and of insulin administration upon fatty acid synthesis have been sufficiently impressive to suggest to many workers that herein lay a second point of action of insulin. The possibility has been entertained that, in addition to its effect upon glucose, insulin exerted some independent stimulatory effect upon the synthesis of fatty acids from two-carbon fragments such as acetic acid.

When a normal, well-nourished animal is utilizing glucose in abundance, a very considerable fraction of all the glucose utilized is each day transformed into fatty acid.[16] To accomplish this end the six-carbon sugar must be broken down by the process of glycolysis to the three carbon acid, pyruvic acid and this compound loses CO_2 to yield the active two-carbon fragment which is today recognized as acetyl-coenzyme A. This two carbon fragment is on the one hand oxidized via the citric acid cycle to CO_2, and on the other hand it serves as a precursor for the synthesis of long-chain fatty acids, a process requiring numerous reductive steps.

If a normal animal is fasted, lipogenesis, the synthesis of fatty acids, is markedly slowed down. This has been demonstrated not only in the intact animal[17] but also in the liver slice[18] from which it may be concluded that the retardation of lipogenesis need not stem from lack of insulin. In studies reported by Chaikoff and his collaborators[19] the ability of diabetic liver slices to generate fatty acids from acetic acid has been compared under various conditions of nutrition. It has been found that whereas little lipogenesis was observed in preparations of liver derived from diabetic animals pre-fed with glucose, essentially normal lipogenesis occurred if the animal had previously been fed fructose. It has long been recognized that the ability to utilize fructose, in contrast to glucose, is independent of insulin supply and it could be concluded that the requisite for lipogenesis was not insulin as such but rather the operation of some phase of carbohydrate metabolism, possibly glycolysis. We may therefore formulate fatty acid synthesis as:

$$\text{ACETYL-CO A} \xrightarrow{\text{(GLYCOLYSIS)}} \text{FATTY ACIDS}$$

The intent of this formulation is to suggest that what had earlier been construed as a specific action of insulin may today be attributed to the

occurrence of glycolysis, hence only secondarily related to insulin supply. It may further be postulated that the supply of reducing agents necessary for lipogenesis comes from the oxidation of the products of active glycolysis.

The untreated diabetic patient, besides losing body fat, is frequently in negative nitrogen balance. This has been shown to be, at least in part, a result of impairment of protein synthesis. Krahl[20] has reported that the ability of muscle and of liver to incorporate glycine into peptide linkage is retarded both in diabetes and in fasting. Thus liver slices derived from either fasted or diabetic rats incorporate glycine into glutathione far more slowly than do slices derived from normal, well-nourished rats.

Whereas glutathione synthesis may differ in some regards from protein synthesis, it has served as a useful model for the study of the general problem of peptide bond formation. The specific reaction concerned:

$$\gamma\text{-GLUTAMYLCYSTEINE} + \text{GLYCINE} \xrightarrow{\text{(GLYCOLYSIS)}} \text{GLUTATHIONE}$$

This reaction has been investigated by Bloch and his collaborators[21] who find that adenosine triphosphate serves as the energy source for formation of this peptide bond. The requirements for adenosine triphosphate is well met, however, by supplying glycogen or certain intermediates in the glycolytic sequence. From this it again appears that peptide bond formation, and by extrapolation, protein formation, depends not directly upon insulin supply but rather upon the operation of the glycolytic cycle.

This postulation of these diverse effects of insulin on protein and lipid metabolism permits the physiologist provisionally to assign to insulin one single function. The problem bears a similarity to that faced by the clinician who endeavors if possible to fit all the signs and symptoms presented by the patient into a single diagnosis. In selecting a working hypothesis for insulin action, one is properly tempted toward the simplest hypothesis which is compatible with the known facts, and the simplest hypothesis is the one which attributes to insulin a single function rather than several diverse functions. This function is related to the introduction of glucose into its several intracellular fates but whether insulin operates on a transport or an enzyme mechanism is not certain.

The effects of hypoinsulinism upon fatty acid synthesis and upon peptide bond formation are essentially the same as those produced by fasting. They can at present be accounted for on the same basis, that

glycolysis or its products are essential for fat and protein synthesis in the mammal. Interference with glycolysis, whether by decreased food intake or inadequate insulin supply, results in impeded lipogenesis and proteogenesis. It is this similarity between diabetes and starvation which has given rise to the epigram that "diabetes is starvation in the midst of plenty."

REFERENCES

1. Sanger, F. Fractionation of oxidized insulin, *Biochem. J. 44*:126-28, 1949.
2. Harfenist, E. J. and Craig, L. C. Difference in the quantitative amino acid composition of insulins isolated from beef, pork and sheep glands, *J. Amer. chem. Soc. 74*:4216-17, 1952.
3. Sanger, F. and Tuppy H. Amino-acid sequence in the phenylalanyl chain of insulin; investigation of peptides from enzymic hydrolysates, *Biochem. J. 49*: 481-90, 1949.
4. Sanger, F. and Thompson, E. O. P. Amino-acid sequence in the glycyl chain of insulin (abstract), *Biochem. J. 52*:iii, 1952.
5. Sutherland, E. W. Effect of the hyperglycemic factor and epinephrine on enzyme systems of liver and muscle, *Ann. N. Y. Acad. Sci. 54*:693-706, 1951.
6. Stadie, W. C. The combination of insulin with tissue, *Ann. N. Y. Acad. Sci. 54*:671-83, 1951.
7. Colowick, S. P., Cori, G. T. and Slein, M. W. Effect of adrenal cortex and anterior pituitary extracts and insulin on hexokinase reaction, *J. biol. Chem. 168*:583-96, 1947.
8. Levine, R., Goldstein, M. S., Huddlestun, B. and Klein, S. P. Action of insulin on "permeability" of cells to free hexoses, as studied by its effect on distribution of galactose, *Amer. J. Physiol. 163*:70-76, 1950.
9. Goldstein, M. S., Henry, L., Huddlestun, B. and Levine, R. Action of insulin on transfer of sugar across cell membrane (abstract), *Fed. Proc. 11*: 56, 1952.
10. Stetten, DeW., Jr. and Boxer, G. E. Studies in carbohydrate metabolism; metabolic defects in alloxan diabetes, *J. biol. Chem. 156*:271-78, 1944.
11. Stetten, DeW., Jr. and Klein, B. V. Studies on carbohydrate metabolism; effects of hypo- and hyperinsulinism in rabbits, *J. biol. Chem. 162*:377-82, 1946.
12. Felts, J. M., Chaikoff, I. L. and Osborn, M. J. Insulin and the fate of lactate in the diabetic liver, *J. biol. Chem. 191*:683-92, 1951.
13. Brady, R. O., Lukens, F. D. W. and Gurin, S. Synthesis of radioactive fatty acids in vitro and its hormonal control, *J. biol. Chem. 193*:459-64, 1951.
14. Bloch, K. and Kramer, W. Effect of pyruvate and insulin on fatty acid synthesis in vitro, *J. biol. Chem. 173*:811-12, 1948.
15. Brady, R. O. and Gurin, S. Biosynthesis of labeled fatty acids and cholesterol in experimental diabetes, *J. biol. Chem. 187*:589-96, 1950.
16. Stetten, DeW., Jr. and Boxer, G. E. Studies in carbohydrate metabolism; rate of turnover of liver and carcass glycogen, studied with the aid of deuterium, *J. biol. Chem. 155*:231-36, 1944.
17. Boxer, G. E. and Stetten, DeW., Jr. Role of thiamine in synthesis of fatty acids from carbohydrate precursors, *J. biol. Chem. 153*:607-16, 1944.
18. Lyon, I., Masri, M. S. and Chaikoff, I. L. Fasting and hepatic lipogenesis from C^{14}-acetate, *J. biol. Chem. 196*:25-32 1952.
19. Baker, N., Chaikoff, I. L. and Schusdek, A. Effect of fructose on lipogenesis from lactate and acetate in diabetic liver, *J. biol. Chem. 194*:535-43, 1952.
20. Krahl, M. E. Personal communication.
21. Yanari, S., Snoke, J. and Bloch, K. Enzymatic synthesis of glutathione (abstract), *Fed. Proc. 11*:315, 1952.

HORMONES AND PEPTIC ULCER*

JOSEPH B. KIRSNER

Professor of Medicine, University of Chicago, Chicago, Ill.

INTRODUCTION

THE possible role of hormones in peptic ulcer has been under investigation for at least fifty years. During this time practically all the endocrine glands have been implicated either in the pathogenesis or the treatment of the disease. The present review summarizes the current status of hormonal factors in human peptic ulcer. The experimental observations in animals are reviewed elsewhere.[1]

PITUITARY GLAND

Posterior Pituitary Extracts in Ulcer Therapy: There is no clear rationale for the use of posterior pituitary extract in the treatment of peptic ulcer. The observation of polyuria and nocturia in occasional patients with duodenal ulcer suggested posterior pituitary hypofunction as a factor in the disease.[2] Blotner[3] noted an increased volume of gastric juice and free acidity in six patients with diabetes insipidus. X-rays demonstrated a duodenal ulcer in two of five patients examined roentgenologically. Digestive symptoms are frequent in diabetes insipidus and the incidence of ulcer may be increased, as Blotner suggests; however, objective evidence of this relationship is difficult to obtain because of the small number of cases. We have not been aware of pituitary hypofunction in the observation of approximately 5000 patients with peptic ulcer. Metz and Lackey[2] reported satisfactory results in the majority of patients with duodenal ulcer, receiving posterior pituitary extract intranasally as an adjunct to conventional treatment. These observations have not been confirmed[4] and the use of posterior pituitary powder in the management of peptic ulcer has not been accepted generally. McGavack[5] reported increased ulcer distress in a patient with both diabetes insipidus and peptic ulcer after administration of posterior pituitary extract.

* Presented at the Twenty-fifth Graduate Fortnight of The New York Academy of Medicine, October 17, 1952.

Peptic Ulcer and Disorders in the Region of the Pituitary Gland: Despite numerous individual case reports,[6] the incidence of peptic ulcer in patients with pituitary tumors probably is not excessive.[7] Bastenie et al.[8] did not encounter ulcer among thirty individuals with acromegaly. In a review of 6200 autopsies we[9] found one instance of both duodenal ulcer and chromophobe adenoma of the pituitary. The occasional coexistence of pituitary lesions and ulcer is not unexpected in view of the frequency of peptic ulcer. The ulcers associated with pituitary tumors often are multiple, penetrating lesions, resembling the ulcerations accompanying injury to the hypothalamic area and other regions of the brain,[10] or complicating intracranial operations. The pathogenesis presumably is similar; mechanical irritation of the autonomic nervous centers by the expanding tumor, gastric hypersecretion and hypermotility, vascular disturbances and areas of ischemia digested by the hyperacid gastric juice. The concept of parasympathetic stimulation by an humoral substance secreted by increased numbers of basophile cells in the posterior lobe of the pituitary gland in patients with peptic ulcer remains to be established.

Winkelstein[11] observed rapid growth to an abnormal height, concomitantly with the development of duodenal ulcer in a group of twenty-four boys of puberty-adolescent age. The ulcers were unusually severe; massive hemorrhage occurred in five, perforation in three; and partial gastrectomy was necessary in eleven patients. The "modified giantism" accompanying the ulcers suggested hyperfunction of the anterior lobe of the pituitary as a factor in the genesis of the lesions; however, in the absence of further evidence, the combination of events appears to have been coincidental.

Thyroid Gland

Gastric Secretion: While gastric secretion in patients with hyperthyroidism may vary as in normal persons, the output of acid usually is diminished and the incidence of anacidity is high, ranging from 30 to 50 per cent.[12, 13] Berryhill and Williams[14] reported achlorhydria in 70 per cent of cases with exophthalmic goiter or toxic adenoma; gastric secretion returned to normal after operation in approximately three-fourths of cases. A similar reversal of gastric secretion has been noted by Wilkinson,[15] indicating that the decreased output of hydrochloric acid in hyperthyroidism is attributable to a physiologic or pharmaco-

logic disturbance, perhaps excessive stimulation of the sympathetic nervous system, rather than to anatomic change such as gastric atrophy.

Gastric secretion in hypothyroidism usually is decreased and anacidity is demonstrable in 50 per cent or more of patients. Lerman and Means[16] noted achlorhydria in nine of seventeen persons with myxedema. The response to histamine was reduced or absent in eighteen of the twenty patients with hypothyroidism studied by Bastenie et al.[17] The development of a duodenal ulcer in one patient after correction of the hypothyroidism suggests that the output of acid may increase after restoration of normal thyroid function.

Peptic Ulcer in Man: Gastric and duodenal ulcers have been found at autopsy in patients with toxic goiter; the lesions are similar to the antemortem erosions or ulcerations observed in many debilitating diseases. The clinical incidence of peptic ulcer in hyperthyroidism is not excessive,[18-20] and, indeed, seems to be lower than usual. Gill and Walton[19] observed three instances of hyperthyroidism among 130 ulcer patients. Bastenie and his colleagues[8] found not a single ulcer among 114 patients with hyperthyroidism studied clinically and eight thyrotoxic cases examined at autopsy.

Peptic ulcer is rare in hypothyroidism;[20] the incidence is not known precisely because of the small number of patients and the few definitive studies. Ulcer was not observed among eighty-six patients with myxedema investigated clinically and twelve cases studied at autopsy.[8] We[9] found no reference to hypothyroidism in the records of more than 450 patients with peptic ulcer examined at autopsy. The comparative infrequency of peptic ulcer in hyper- and hypothyroid states would be in accord with the decreased outputs of acid observed under such conditions.

Parathyroid Glands

Hypoparathyroidism and Peptic Ulcer: Grove and Vines[21] in 1922 reported hypocalcemia in twelve patients with gastroduodenal ulcer and recommended treatment with parathyroid extract. Parathyroid hypofunction subsequently was assumed to stimulate the parasympathetic nervous system, causing gastric hypersecretion and hypermotility; other postulated mechanisms included the development of acidosis, interfering with the healing of ulcer, and the precipitation of calcium salts in the gastric wall, decreasing its resistance to acid indigestion.[22, 23] The favor-

able results ascribed to parathyroid extract in the treatment of peptic ulcer are not impressive; relapses are frequent; many patients are not improved,[24] and the transient subjective response may be duplicated or excelled by many non-specific therapeutic measures. Parathyroid extract, in physiologic doses, does not consistently lower gastric secretion in patients with duodenal ulcer. The injection of 1200 to 2200 U. S. P. units during periods up to eleven days diminished the basal gastric secretion occasionally; the response to histamine was not reduced significantly.*[25] Larger amounts of parathyroid extract may be more effective, but they also may produce untoward side effects; in studying the influence of hormonal agents and other compounds upon gastric secretion in man, toxic symptoms must be avoided, since these reactions, per se, may diminish the output of acid.

The serum calcium is normal in patients with uncomplicated peptic ulcer and the differences in gastric secretion between duodenal ulcer and normal persons are not correlated with significant alterations in serum calcium. The tetany now rarely observed in peptic ulcer results from excessive vomiting as a consequence of pyloric obstruction, and depletion of serum electrolytes; it is not attributable to primary parathyroid hypofunction. Peptic ulcer seems to be rare in hypoparathyroidism;[26] Steinberg and Waldron[27] reported not a single instance of ulcer in a careful review of fifty-two cases of primary hypoparathyroidism recorded in the literature.

Hyperparathyroidism and Peptic Ulcer: Peptic ulcer is not uncommon in patients with primary or secondary hyperparathyroidism.[26, 28-30] The co-existence of the two diseases is not always recognized. Läuchli[29] found gastroduodenal ulcers, not suspected clinically, in five of six patients with hyperparathyroidism examined at autopsy. Since the ulcer may antedate the parathyroid disturbance by many years, the prolonged, excessive ingestion of milk and alkali has been implicated in the process; however, the mechanism is not apparent. Excessive intakes of absorbable calcium depress parathyroid activity; there is no reliable evidence that phosphates stimulate parathyroid function. The hyperparathyroidism in some cases probably is attributable to renal disease and secondary stimulation of the parathyroids.

A related syndrome, noted infrequently in patients with peptic ulcer,

* These and similar studies reported in this paper were supported in part by a grant from the United States Public Health Service.

is characterized by hypercalcemia without hypercalcuria or hyperphosphatemia, normal serum alkaline phosphatase, severe renal insufficiency, mild alkalosis and calcinosis.[31, 32] We have observed this entity in a small group of ulcer patients with hypertension and pre-existing renal impairment; the alkali usually has consisted of sodium bicarbonate.[32] The sequence of events, according to Burnett and his associates,[31] seems to be renal damage, fixation in urinary calcium excretion and a tendency to supersaturation with calcium phosphate; however, parathyroid hyperfunction cannot be completely excluded. Improvement occurs gradually when the intake of fluid is increased and the milk and alkali are discontinued. Gastric secretion in patients with hyper- or hypoparathyroidism or the effects of parathyroid hormone upon the gastroduodenal mucosa have not been investigated systematically; such studies would be of considerable interest, especially in relation to peptic ulcer and hyperparathyroidism. We have observed moderate quantities of hydrochloric acid in the gastric content of one patient with primary hyperparathyroidism.

Pancreas

Diabetes Mellitus: The incidence of peptic ulcer in diabetes mellitus is not known precisely, although it is higher than has been assumed.[33, 34] Joslin[35] found not a single ulcer among his first 2700 cases; Wilder[36] reported 61 cases among 2584 diabetics (2.3 per cent) and Wood[37] noted 94 instances among 12,000 diabetics (0.78 per cent). The more frequent roentgen examination of diabetics with digestive symptoms undoubtedly would reveal a higher incidence than these figures would suggest. It is our impression that peptic ulcer occurs with similar or perhaps slightly decreased frequency in diabetics as in non-diabetic patients of the same age. Gastric analyses, utilizing chiefly the Ewald or similar test meals, have indicated a decreased output of hydrochloric acid in the majority of patients with diabetes mellitus, and achlorhydria in approximately 30 per cent of cases.[38] The gastric secretion of diabetics should be re-studied with histamine, caffeine or other powerful secretory stimulants and compared with the response of individuals in the same age groups. Diabetics with duodenal ulcer secrete as much hydrochloric acid as the non-diabetic with duodenal ulcer.

Insulin Hypoglycemia and Peptic Ulcer: There is no satisfactory rationale for the use of insulin in the treatment of peptic ulcer[39] and

the favorable clinical reports are not convincing.[40] There are no objective data for the assumptions that insulin decreases vagal activity, "alkalinizes" the blood or improves gastric circulation. The hypoglycemia induced by insulin administered intravenously stimulates the vagus centers and the brain generally, thereby increasing the output of hydrochloric acid. The gastric secretory response to insulin is greater in patients with duodenal ulcer than in normal persons,[41] perhaps because of hyperactivity of the vagus centers in the brain or hyperreactivity of the parietal cells peripherally. Peptic ulcer is not more common in diabetics taking insulin than in diabetics regulated by diet. The insulin therapy of diabetes mellitus avoids hypoglycemia and, therefore, should not predispose to the formation of ulcer.

Chronic hypoglycemia is not present in patients with peptic ulcer and there is no conclusive evidence that hyperinsulinism is an important factor in the pathogenesis of peptic ulcer.[42] The differences in gastric secretion between patients with duodenal ulcer and normal persons have not been correlated with demonstrably significant fluctuations in the blood sugar. Peptic ulcer seems to be quite rare in patients with islet-cell tumors of the pancreas and prolonged severe hypoglycemia. Crain and Thorn,[43] in a review of 258 cases reported up to 1949, do not mention ulcer as a complication. Our records contain one instance of peptic ulcer and islet-cell tumor of the pancreas. In the single case described by Janowitz and Crohn,[44] removal of the adenoma and surgical cure of the hypoglycemia had no ameliorating effect upon the clinical course of the duodenal ulcer.

Gastrointestinal Hormones

Antrum Mechanism and Gastrin: Gastric secretion is stimulated, in part, by the hormone, gastrin, produced by the mucosa of the antrum of the stomach in response to mechanical and chemical stimuli.[45, 46] The chemical identity of gastrin is not yet established. The experimental observations of Dragstedt and his colleagues[47] indicate that the antrum plays a vital role in the gastric secretion of dogs and, under certain experimental conditions, may increase greatly the output of acid and cause gastroduodenal or gastrojejunal ulcers. The role of the antrum mechanism in normal human gastric secretion remains to be established. There is no conclusive evidence as yet that hyperactivity of the antral mechanism is involved in the gastric hypersecretion characterizing

patients with duodenal ulcer. Removal of the antrum during partial gastrectomy is alleged to contribute to the decreased gastric secretion postoperatively; however, the increased outputs of acid may persist in duodenal ulcer despite complete resection of the antrum.[48]

Enterogastrone is the hormone produced by the mucosa of the upper portion of the small intestine in the presence of fat, and is responsible physiologically for the decrease in gastric secretion and motility after the ingestion of fat.[49] Enterogastrone administered orally or parenterally, in single or repeated doses, does not significantly or consistently inhibit gastric secretion and motility in man.[50-52] Fewer recurrences of peptic ulcer were observed initially in patients undergoing prolonged treatment with enterogastrone; subsequent results were less encouraging.[53] In other studies, enterogastrone, intramuscularly or by mouth, did not influence the course of peptic ulcer favorably.[54] Further investigation with more purified concentrates should be of interest. However, there is no satisfactory evidence that patients with peptic ulcer lack the enterogastrone isolated from hog's intestine or that the hypersecretion of duodenal ulcer is caused by a disturbance of the enterogastrone mechanism.

Extracts of Animal Stomach and Intestine: The treatment of peptic ulcer with extracts of animal stomach and intestine currently is popular in Europe.[55-61] Two materials are prescribed. The water-soluble fraction, free of protein and administered parenterally; and the water-insoluble fraction, taken orally. Favorable therapeutic results have been reported frequently. However, many patients are not benefited; the improvement often is temporary; and relapses are frequent.[62, 63] Further studies of the chemical nature, biologic behavior and mode of action of these tissue extracts are necessary before the rationale for their use and their therapeutic usefulness can be evaluated accurately.

Urogastrone is the term applied to a substance extractable from the urine of man and animals, capable of inhibiting the gastric secretory response to food, histamine and insulin in man and animals when admintered intravenously. It is found in the urine of pregnant and nonpregnant females, normal men and patients with gastric ulcer, duodenal ulcer, pernicious anemia, and carcinoma of the stomach.[64, 65] The chemical identity of urogastrone is unknown and its status as a hormone is uncertain. Urogastrone from normal male urine decreases basal and histamine-stimulated secretion in human subjects, apparently without

rise in temperature or systemic reaction.[66] However, the subcutaneous or intramuscular injection of quantities thirty times larger than the effective intravenous dose for dogs failed to inhibit the nocturnal gastric secretion in ulcer patients.[67] The significance of urogastrone in peptic ulcer is not known. Present preparations are not suitable for use in man and further clinical studies await isolation, purification and identification of the active principle.

Adrenal Glands

Addison's Disease and Peptic Ulcer: Chronic peptic ulcer is uncommon in Addison's disease. Marañon[68] and his associates noted only three verified ulcers among 160 patients with Addison's disease, including twenty-five cases examined at autopsy. Bastenie and his colleagues[8] did not report a single ulcer among thirty-eight patients with Addison's disease studied clinically and twenty cases examined at autopsy. Turner[69] observed acute gastroduodenal erosions and ulcerations at autopsy in four of twenty-nine patients; a chronic ulcer in one case antedated the adrenal insufficiency developing terminally after massive invasion of the adrenals by tumor. The infrequency of chronic peptic ulcer in Addison's disease coincides with the decreased outputs of hydrochloric acid observed in such cases.[70, 71] In Soffer's[72] experience, patients during an acute adrenal crisis may develop shallow, superficial ulcerations, particularly in the pyloric region of the stomach, first portion of the duodenum, the jejunum and occasionally in the rectum. The lesions heal promptly when adrenal function is restored by appropriate treatment and are not evident roentgenologically after the patient recovers from the crisis.

DOCA in Treatment of Peptic Ulcer: The treatment of peptic ulcer with desoxycorticosterone acetate is based upon the assumption that adrenal hypofunction is a major factor in the development of the disease. The favorable clinical results have been ascribed theoretically to improvement in gastric circulation and capillary resistance, detoxification of histamine or to the relief of tissue anoxia.[73, 74] These concepts are unsupported by objective data and the clinical results are not entirely convincing.[40, 75-78] The subjective improvement usually is of brief duration; recurrences are frequent; and many patients do not improve, even temporarily. Furthermore, there is no satisfactory evidence of adrenal hypofunction in uncomplicated peptic ulcer. The reports of positive

water and potassium tests[78] and the decreased outputs of 17-ketosteroids are inconclusive. The excretion of 17-ketosteroids diminishes in many chronic, nutritionally depleting gastrointestinal diseases, unrelated to peptic ulcer, such as cancer, sprue, ulcerative colitis and hepatic disease.[79] According to de Muro,[80] large quantities of desoxycorticosterone acetate decrease the output of acid in normal persons; however, the antisecretory effect is much less definite in patients with peptic ulcer. The injection of DOCA, in total doses of 25 to 45 mg., may decrease temporarily the basal secretion in a few patients with duodenal ulcer; the response to histamine is unchanged.[24] Negative or variable results in man have been reported also with whole adrenal cortical extract and with epinephrine.[81]

Adrenocortical Function in Peptic Ulcer: The occurrence of peptic ulcer during the prolonged administration of corticotropin or cortisone has stimulated interest in the possible role of adrenal hyperfunction in the pathogenesis of the disease. At present, there is little information concerning adrenal function in peptic ulcer. Sandweiss and his associates[82] noted, in patients with active duodenal ulcer, a significant decrease in the output of 11-oxycorticosteroids and a slight rise in the average excretion of 17-ketosteroids, suggesting adrenocortical hyperactivity. Turner[83] reported subnormal responses to the four-hour eosinophile test in forty-one of forty-three ulcer patients given epinephrine, ACTH or both; the results were considered compatible with a disturbance of the pituitary-adrenal system, perhaps temporary exhaustion; and suggested the possibility of acute erosions and ulcerations developing during transient phases of acute adrenal exhaustion. Best et al.[84] have questioned the significance of single eosinophile tests and also the validity of the epinephrine or ephedrine procedures for estimating the functional capacity of the hypothalamic-pituitary-adrenal system. Adrenal function in peptic ulcer obviously requires much more investigation; in gastric ulcer as well as duodenal ulcer; in the same patient during and after various complications; and in comparison with adrenal function in other diseases. Such studies may help clarify the relative importance of peptic ulcer evoking the "stress response" and stress producing the ulcer.

Corticotropin, Cortisone–Gastric Secretion, Peptic Ulcer: Single average doses of corticotropin or cortisone do not alter basal gastric secretion in man.[85] However, the prolonged administration of large

quantities of these steroids may increase greatly the volume of gastric secretion, free acidity and peptic activity;[86, 87] the rise may be from normal values to levels characteristic of duodenal ulcer. Similar effects may be observed also after complete gastric vagotomy. The excretion of urinary uropepsin, a proteolytic enzyme originating in the pepsinogen secreted by the stomach,[88] also may rise,[86, 89] paralleling the increase in urinary nitrogen. The frequency with which corticotropin or cortisone stimulates gastric secretion is not known since gastric analyses are not performed routinely during adrenal steroid therapy. However, the incidence of ulcer seems comparatively low in relation to the large numbers of patients treated with the adrenal hormones.[86, 90] The ulcers are acute, penetrating craters, often complicated by hemorrhage or perforation; the histologic appearance is that of a corrosive rather than an inflammatory or vascular process. There may be no history of preexisting digestive symptoms. The ulcers seem attributable chiefly to the excessive outputs of acid and pepsin, induced by corticotropin or cortisone, and perhaps to damaging effects of the steroids directly upon the stomach and duodenum.

The clinical observations have suggested the concept that stress, whether emotional or physical in origin, induces the hypothalamus to secrete an humoral agent stimulating the pituitary secretion of ACTH. The corticotropin then acts upon the adrenal glands releasing cortisone and other steroids, stimulating the gastric glands to secrete acid and pepsin. The hypothesis provides an attractive explanation for the ulcers produced experimentally under varying conditions of stress. However, the presence of the adrenal glands or the hypophysis is not necessary to the development of gastrointestinal lesions during the alarm reaction.[91] The concept also offers a plausible mechanism for the ulcers developing in man after prolonged emotional conflict. However, much more information concerning the status of the hypothalamus-pituitary-adrenal system in peptic ulcer and perhaps also the role of sympathetic-adrenal activity is necessary to determine the general applicability of this thesis. Peptic ulcer seems to be rare in patients with hyperfunction of the adrenal cortex of the adrenogenital type and in children and adolescents with Cushing's syndrome.[92, 93] Levine[92] has not encountered peptic ulcer in eleven patients with Cushing's syndrome. Since hyperactivity of the hypothalamus-pituitary-adrenal axis presumably increases the output of hydrochloric acid, the concept would seem less applicable to

gastric ulcer, characterized by subnormal gastric secretion, than to duodenal ulcer. Dragstedt and his colleagues[94] point out that if the hypersecretion in duodenal ulcer is caused by the adrenal stress mechanism, and since cortisone stimulates acid output in the absence of vagal connections, the excessive secretion might be expected to continue after vagotomy. On the contrary, complete gastric vagotomy in patients with duodenal ulcer restores gastric secretion to approximately normal levels, suggesting that the hypersecretion is caused by excessive secretory stimuli over the vagus nerves and not by the liberation of cortisone from the adrenal glands.

Sex Glands

Sex Incidence of Peptic Ulcer: Peptic ulcer seems to be uncommon during childhood,[95, 96] although recent surveys suggest a higher incidence than had been assumed;[97] ulcers developing in this period of life occur with approximately equal frequency among males and females. After puberty, the incidence rises in both sexes, but the increment is much greater in males. During adult life, gastric ulcer is three or four times more prevalent and duodenal ulcer nearly ten-fold more common among men than women.[98-101] A similar trend is indicated by mortality statistics for the United States (1934-44), Great Britain (1927-1937), Sweden (1932-1944), and Switzerland (1927-1930), compiled by Ivy and Martin.[102] In this analysis, the proportion of male to female deaths from all causes remained constant throughout all age groups at approximately 1.2; that is 12 male fatalities for every 10 female deaths. For peptic ulcer up to fourteen years of age the ratio of male to female deaths was the same as for all diseases. The ratio increased to 2.8 during the age period fifteen to nineteen and to 4.2 between the years of twenty and twenty-nine. The male predominance was maintained until approximately the age of sixty; the ratio then decreased, presumably because of the increased frequency of ulcer in women after the menopause. Collins, Phillips and Oliver,[103] by household interviews, surveyed the incidence of disabling sickness among families in the Eastern Health District of Baltimore during the period 1938-1943. Case rates for the majority of illnesses, including diseases of the thyroid and parathyroids, digestive disturbances and nervousness were higher in females; males predominated in peptic ulcer, chronic bronchitis, hernia and in most types of accidents. In addition to lower incidence, the disease seems to

be less severe in women than in men and accompanied by fewer complications.

The sex differences in peptic ulcer have not been adequately explained. The presumably greater exposure of men to environmental influences predisposing to ulcer and the development of ulcers in women subjected to comparable or similar tensions, suggest the role of emotional factors. The possible deleterious effects of the androgenic hormones remain to be investigated. The possible protective influence of female sex hormones thus far has not been established. The course of peptic ulcer in women during various phases of the reproductive period might be expected to provide information pertinent to this question.

Menstruation and Ulcer: Menstruation seems to have no consistent influence upon the symptoms of peptic ulcer.[104] The many biologic and psychologic changes during this period preclude emphasis of any single factor. The decreases in gastric secretion noted by several investigators during the menses,[105, 106] suggested to Hellebrandt and Brogdon[106] the possible role of the corpus luteum hormone, progesterone.

Pregnancy and Peptic Ulcer: Approximately 10 to 20 per cent of ulcers during adult life occur in women. Nevertheless, active ulcer is rarely diagnosed during pregnancy.[98, 107-112] Jones[111] found not a single instance among 10,000 pregnancies; one patient experienced a slight hematemesis but ulcer was not demonstrated. Peptic ulcer also was not encountered among 2,000 women with abortions admitted to the hospital during the same period. Sandweiss[113] noted only one chronic ulcer in the records of more than 70,000 pregnancies. Peptic ulcer probably is more common during gestation than these figures would indicate. The retrospective analysis of records is not a wholly satisfactory method for establishing the incidence of a disease such as peptic ulcer, requiring for diagnosis, a careful history, gastric analysis, and roentgen examination. The more frequent roentgen examination of pregnant women with digestive symptoms undoubtedly would increase recognition of the disease. Nevertheless, the general impression of lowered incidence of active ulcer in pregnancy seems acceptable on the basis of present evidence.

In female patients with ulcer distress, symptoms often subside coincident with the onset of gestation. Szenes [108] reported improvement in thirteen of nineteen females under these circumstances. Among twenty-five women with proved ulcers and observed through one or more

pregnancies, only one continued to experience ulcer distress; a second pregnancy in this patient was uneventful. Chavarri and his colleagues[114] describe the interesting case of a woman with duodenal ulcer, not responding to conventional methods of therapy, in whom symptoms subsided only during pregnancy; the patient experienced remissions during each of seven pregnancies; gastric resection finally was performed for recurrent, uncontrollable distress two years after the seventh gestation. In addition to the hormonal aspects, this case would appear to present interesting possibilities for psychiatric interpretation. We observed one pregnant female in whom ulcer symptoms persisted until the last trimester.

The recurrences of peptic ulcer complicating gestation[115-119] are more frequent in the final trimester than during the initial six months. Bleeding and perforation are not uncommon and the course of the disease may be severe. We have encountered at least two patients with hemorrhage from peptic ulcer in the latter months of pregnancy; similar cases have been recorded by others. The postpartum period seems to be especially hazardous; Sandweiss collected from the literature thirteen instances of fatal hemorrhage or perforation, complicating ulcer during the puerperium. In two of the four cases described by Bralow et al.,[119] bleeding from ulcer occurred five and ten days after delivery.

Pregnancy and Gastric Secretion: The tendencies for peptic ulcer to heal early in pregnancy and for the lesion, if it recurs, to relapse late in gestation appear to be correlated with appropriate variations in gastric secretion. The output of hydrochloric acid decreases during the first and second trimesters of pregnancy.[108,120,121] Strauss and Castle[122] measured the gastric secretory response to alcohol or histamine in twenty-four pregnant women each month of gestation and again ten days after delivery. Persistent histamine-anacidity was present in three cases. The outputs of acid and pepsin were reduced in fifteen, and were normal in six patients. The decreases were most pronounced between the 140th and 200th days of pregnancy. Gastric secretion increased during the ninth month; seventeen of the twenty-one women without anacidity produced much more acid after delivery than during pregnancy. Labata[123] reported low outputs of acid, returning to normal after delivery, in only nine of fifty-six pregnant women. Histamine anacidity was present in five cases; acid reappeared in two after pregnancy was concluded. Gastric acidity was normal in the remaining forty-two patients, but most of these were in the final trimester or last month of gestation. Way[124] found an inverse

correlation between gastric acidity and the urinary excretion of anterior pituitary-like hormone during pregnancy; the lower gastric acidity early in gestation was correlated with high excretion levels of chorionic gonadotropin; the augmented acidity late in pregnancy accompanied the abrupt decline in chorionic gonadotropins. The increased gastric secretion late in pregnancy and during the puerperium also may be related, in part at least, to intensified adrenal activity at this time.[125]

Menopause and Peptic Ulcer: Peptic ulcers in women often develop or recur with the onset of natural or artificial menopause.[126,127] The possible changes in gastric secretion accompanying the menopause have not been investigated. Such studies might be of considerable interest in relation to the effect of sex hormones upon the output of acid. Hyperactivity of the anterior lobe of the pituitary gland, deficiency of estrogens and other hormonal imbalances may be implicated in the "menopausal ulcers" of women. However, in evaluating these factors, the important role of the emotional disturbances accompanying the menopause should not be underestimated.

The recognizable fluctuations in sex hormones during the various phases of the female reproductive period chiefly involve estrogens, chorionic gonadotropin and progesterone. Studies of the possible relationship between sex, gastric secretion and peptic ulcer have dealt chiefly with these three hormones.

Estrogen Therapy of Peptic Ulcer: Estrogens have been used extensively in the treatment of peptic ulcer during the last fifteen years, especially in Europe. Varying quantities of Progynon-B, estradiol benzoate, stilbestrol, or other estrogens have been administered intramuscularly alone, together with androgens or vitamins, and as an adjunct to therapy with diet and antacids. A surprisingly large number of favorable reports[128-137] have emphasized the increased sense of well-being and prompt relief of ulcer distress, especially in patients with gastric ulcer, in males, and in women during the menopause. The clinical reports are not impressive for several reasons: the relatively brief periods of observation, the concomitant use of other therapeutic measures, and the lack of adequate controls. The favorable results have been observed chiefly in early uncomplicated cases, likely to respond to any therapy, including the injection of inert materials. Many reports[127,130,138-142] emphasize the transitory symptomatic improvement and the frequent relapses. In one series of forty-four patients, "prolonged" recovery occurred in only four cases.[140]

Hemorrhage and perforation are not prevented; indeed, several observers have emphasized the intensification of ulcer bleeding during estrogen therapy. Meeroff[143] refers to the development of the hepatorenal syndrome after the administration of huge quantities of estrogen (0.5 mg. per kilo body weight).

Most studies indicate that estrogens do not decrease gastric secretion significantly in patients with peptic ulcer.[25, 128, 142, 144] Ojha[137] reported a reduction in the free acid values and concurrent clinical improvement in six male patients with duodenal ulcer after the administration of 10 mg. of stilbestrol daily for ten days; the decreases ranged from 22 to 60 per cent of the control values. Abrahamson and Hinton[142] observed an increased response to histamine in patients with duodenal ulcer after the repeated injection of theelin. We[25] obtained no significant decrease in the twelve hour nocturnal gastric secretion after 30,000 R. U. of Progynon B; or in the one hour basal and histamine-stimulated secretion after 30 to 60,000 R. U. had been injected. Progesterone alone and together with estrogens also had no appreciable effect. The quantities of estrogen administered in these experiments may be too small to warrant final conclusions and further studies with larger amounts probably are desirable.

There is no satisfactory objective evidence that estrogens improve the resistance of the gastric mucosa to acid digestion. The beneficial effects attributed to the gastric hyperemia following the use of estrogens[129] have not been proven. The increased fibroblastic activity and other signs suggesting healing in the resected stomach of five patients undergoing operation after the use of estrogens[145] are not specific to the hormonal treatment; all ulcers manifest a natural tendency to healing, especially when protected from acid gastric juice. The histologic appearance of the stomach was normal in three patients with duodenal ulcer requiring operation after failure of estrogen therapy.[142]

Chorionic Gonadotropin–Human Gastric Secretion: Chorionic gonadotropin, in ordinary amounts, does not inhibit gastric secretion in man consistently.[25, 113, 146, 147] The responses to histamine and insulin decreased moderately in a male patient with duodenal ulcer after the injection of chorionic gonadotropin in quantities corresponding to 2 mg. of the extract from pregnancy urine.[148] We[25] occasionally observed transient decreases in the output of acid among male patients with duodenal ulcer after 5000 I. U. had been administered. The combination of chorionic gonadotropin with estrogens or with serum gonadotropins also

lowered gastric secretion occasionally; repeated administration of these hormones for periods up to one week did not alter basal or histamine-stimulated secretion. The inconsistent and unimpressive results may be related to differences in potency of the chorionic gonadotropin and to inadequate dosage.

Chorionic Gonadotropin–Uroanthelone Therapy in Peptic Ulcer: The favorable results obtained with chorionic gonadotropin or with uroanthelone in the management of experimental ulcer in the dog have not been reproduced clinically. Symptoms subsided in sixty-three patients treated with uroanthelone from human pregnancy urine, but relapses were not prevented.[97, 149] Favorable clinical results were described with an extract of pregnant mares' urine,[150] apparently devoid of estrogenic or gonadotropic activity, without effect upon gastric secretion[151] and prolonging the survival of Mann-Williamson dogs. However, more recent clinical observations are less encouraging[149] and the status of uroanthelone therapy in peptic ulcer remains in doubt.

Comment

The present survey of hormonal factors in peptic ulcer indicates no consistent relationship between primary endocrine diseases and chronic peptic ulcer in man. Many studies are speculative, inconclusive and lack objective data. Definitive analysis of the subject is handicapped further by lack of knowledge of all the factors contributing to the formation of peptic ulcer, and by incomplete understanding of the numerous functional inter-relationships between endocrine glands as well as between endocrine activity and the autonomic nervous system. Nevertheless, sufficient evidence is available perhaps to define the problem more clearly and to indicate those aspects requiring further investigation.

The experimental observations in animals are of interest in demonstrating the influence of profound alterations in endocrine function upon the gastrointestinal tract. However, the results are of limited clinical applicability because of species differences, the highly artificial nature of the experiments and the multiple effects, known and unknown, accompanying even the simplest procedures. The gastrointestinal tract of animals is extremely sensitive to a variety of conditions currently identified as stress. Multiple hemorrhages, erosions and superficial ulcerations may be induced by many "non-specific" stimuli. The lesions occur

not only in the stomach and duodenum, but elsewhere in the digestive tract. The pathogenesis of the erosions and ulcerations is believed to involve the release of ACTH from the anterior lobe of the pituitary gland, and the stimulation of adrenal cortical function, with deleterious effects upon the stomach and duodenum. Similar lesions may develop in the absence of the hypophysis or adrenal. The ulcerations occurring under these circumstances have been attributed to decreased tissue resistance, and increased autonomic activity, stimulating gastrointestinal secretory, motor and vasomotor functions. The gastroduodenal erosions and ulcerations accompanying removal of the pituitary, thyroid, parathyroid or adrenal glands are identical with the lesions produced by "non-specific" stimuli and thus do not constitute evidence of endogenous endocrine hypofunction as a cause of peptic ulcer. The erosions and ulcerations induced by posterior pituitary extract develop on a similar basis, abetted by the peripheral constrictive action of the vasopressor fraction; similarly, they do not signify endogenous pituitary hyperfunction as an etiologic factor in peptic ulcer. The endocrine ablation experiments obviously are not pertinent to the clinical problem; man, with rare exceptions, develops his ulcer in the presence of intact pituitary, thyroid, parathyroid and adrenal glands.

Ingenious experimental techniques have demonstrated significant effects of the gastrointestinal hormones, gastrin and enterogastrone, in the dog; similar influences have not been established in man. Hyperfunction of the antrum mechanism, induced by transplantation of this structure to the colon, causes increased production of gastrin, sustained gastric hypersecretion and the development of penetrating gastro-jejunal ulcers. There is no conclusive evidence of antrum hyperfunction in patients with peptic ulcer. Removal of the antrum during gastric resection for duodenal ulcer does not necessarily decrease the excessive output of acid. On the other hand, successful gastric vagotomy restores gastric secretion approximately to normal, suggesting that the hypersecretion is vagal in origin. The role of gastrin in the normal gastric secretion of man remains to be determined.

Enterogastrone inhibits gastric secretion in dogs when administered intravenously; other routes of administration are not effective. The favorable results observed initially with enterogastrone in the treatment of Mann-Williamson ulcers suggested a similar applicability in man. However, numerous studies have failed to demonstrate consistently

significant inhibition of gastric secretion or sustained improvement in the course of peptic ulcer. The favorable results in dogs were obtained after intravenous injection; the ineffective results in man followed the oral or intramuscular administration of enterogastrone. It will be of interest, therefore, to re-investigate the problem when more purified preparations suitable for intravenous use are available. However, there is no satisfactory evidence of an enterogastrone deficiency in peptic ulcer.

Endocrine disorders, if important in the pathogenesis of peptic ulcer, should be demonstrable in at least two ways: evidence of endocrine dysfunction, clinically or by laboratory measurement, in a significant percentage of ulcer patients or objective evidence of ulcer in a significant number of patients with the endocrine disorder. Although systematic studies of this type have been made only occasionally, extensive clinical observation demonstrates no conspicuous correlation in either direction. Bastenie and his colleagues reported not a single ulcer in approximately 300 patients with various endocrine diseases. Preliminary analysis of the records of more than 450 patients with peptic ulcer examined at autopsy at the University of Chicago disclosed twenty-seven with diabetes mellitus, six with hyperthyroidism and miscellaneous endocrine disorders in only four additional cases. With regard to individual endocrine glands, present evidence suggests no significant relationship between chronic peptic ulcer and primary diseases of the pituitary or the pancreas. The decreased incidence of ulcer in hypothyroidism and hyperthyroidism coincides with the diminished gastric secretion observed in the majority of patients with these disorders.

Peptic ulcer seems to be rare in hypoparathyroidism and not uncommon in hyperparathyroidism; yet, in the dog, hypocalcemia tends to increase the output of hydrochloric acid and hypercalcemia tends to reduce the nervous phase of gastric secretion. This seemingly paradoxical relationship cannot be explained at present. The clinical observations, though not conclusive, are sufficiently interesting to warrant investigation of parathyroid function in peptic ulcer, and gastric secretory studies and roentgen examination of the stomach and duodenum in patients with parathyroid disease.

There appears to be no striking relationship between chronic peptic ulcer and primary diseases of the adrenal glands. Gastric secretion is decreased in Addison's disease and chronic ulceration is rare. The ulcers

complicating adrenal crises are acute superficial lesions, not necessarily limited to the stomach or duodenum; they heal rapidly with restoration of adrenal function. There is no satisfactory evidence of adrenal hypofunction as a factor in the pathogenesis of peptic ulcer; consequently, there is no obvious rationale for therapy with DOCA or other adrenal cortical hormones.

Since pregnancy apparently benefits peptic ulcer as well as rheumatoid arthritis, the favorable influence of corticotropin and cortisone in arthritis suggested the possibility of a similar usefulness in ulcer. On the contrary, there is now sufficient experience to indicate that these adrenal hormones may greatly increase gastric acidity and peptic activity and thereby precipitate the recurrence or new development of peptic ulcer. However, there is insufficient evidence at present to justify the current emphasis upon the "adrenal stress mechanism" in all peptic ulcers. The incidence of gastroduodenal ulcers complicating adrenal steroid therapy, so far as can be determined from the literature, seems relatively low in comparison with the huge number of patients receiving corticotropin or cortisone. Many individuals with peptic ulcer probably have received the adrenal steroids for other concomitant illnesses, without apparent untoward effects. Peptic ulcer seems to be rare in adrenocortical hyperactivity of the adrenogenital type. There is no satisfactory evidence of an increased incidence of ulcer in Cushing's syndrome. Much more information obviously is needed to evaluate fully the role of ACTH-induced adrenocortical hyperactivity in the pathogenesis of peptic ulcer. Many interesting problems await investigation; these include, evidence for primary endogenous adrenocortical dysfunction in duodenal ulcer; the specificity of ACTH-stimulation of the adrenal cortex; the possible damaging effects of corticotropin and cortisone directly upon the gastroduodenal mucosa; gastric secretory studies and roentgen surveys of patients with adrenal diseases, especially those characterized physiologically by hypersecretion of corticoids; and careful, prolonged study of adrenal function in patients with peptic ulcer, gastric as well as duodenal. These investigations and related studies should greatly clarify the relative importance of stress producing ulcer and ulcer evoking stress.

The sex differences in peptic ulcer present an equally intriguing problem for further investigation; although much of the information is suggestive rather than conclusive. The possible role of the androgens

in increasing the susceptibility to the disease remains to be investigated. The comparatively low incidence of ulcer in adult women during the active reproductive period, the apparent healing of ulcer early in pregnancy, and the frequency of ulcer after the menopause suggest a protective influence of the female sex hormones. Theoretically, the beneficial effects of the female sex hormones should be manifested either in a decreased gastric secretion or improved resistance of the gastroduodenal mucosa to acid digestion. Decisive evidence in support of this relationship has not appeared thus far. Women generally secrete smaller quantities of hydrochloric acid than men; but gastric secretion in women with duodenal ulcer often exceeds the average output of acid in normal males. The lowered gastric acidity early in pregnancy, concomitantly with clinical improvement, seems to parallel the pronounced increase in chorionic gonadotropins and the higher concentrations of progesterone and estrogens. The elevated outputs of urinary glucocorticoids and 17-ketosteroids late in gestation indicate that hormones originating in the hyperactive maternal adrenals or possibly in the placenta also contribute to this increased gastric secretion; the endocrine performance of the fetal adrenal cortex and its role in this situation are not known. Direct studies of the effect of sex hormones upon the output of acid in man thus far have been inconclusive or negative. Chorionic gonadotropins administered alone or with estrogens and serum gonadotropins, diminish gastric secretion temporarily in occasional patients with duodenal ulcer; anacidity does not occur and the decreases are not impressive.

With the possible exception of chorionic gonadotropin and uroanthelone in the treatment of Mann-Williamson ulcers in dogs, there is no convincing evidence of improved resistance of the gastroduodenal mucosa following the administration of sex hormones. Furthermore, the Mann-Williamson ulcer is not entirely suitable for the study of a problem, such as this, requiring direct investigation in man. Many clinical reports, especially those dealing with estrogens, are based upon brief periods of observation, inadequate controls and the observation of uncomplicated ulcers, likely to respond to a variety of therapeutic measures. The concurrent use of other methods of treatment and the "spontaneous" fluctuations in the course of peptic ulcer unrelated to medication, further diminish the significance of the observations. The negative findings, nevertheless, do not entirely dispose of the problem

of sex hormones and ulcer. Experimental and clinical studies have not reproduced the hormonal patterns of the pregnant and non-pregnant female. The quantities of hormones administrated thus far have been comparatively small. It would seem desirable, therefore, to investigate the problem in greater detail. More data are needed to confirm the apparent beneficial influence of pregnancy upon the clinical course of peptic ulcer. Studies of the gastric secretory patterns and roentgen examination of the stomach and duodenum in eunuchs would be of related interest, if a sufficient number of cases were available. Other projects might include systematic investigation of the effects of maximal, yet clinically tolerable, quantities of sex hormones, both male and female, upon gastric secretion; comparison of the gastric mucus secretion in men and in pregnant and non-pregnant females; the beneficial influence of chorionic gonadotropin and uroanthelone upon Mann-Williamson ulcers; and identification of the factors in urine decreasing gastric secretion and presumably protecting against experimental ulcer. In addition to these studies of more or less direct hormonal effects, investigation also might be made of the indirect or "permissive" action of hormones upon processes possibly implicated in the pathogenesis of peptic ulcer. The solution to these and the other previously noted problems by objective analysis and fundamental research may be expected to eliminate much of the speculation and empiricism now obscuring the status of hormones in chronic peptic ulcer.

REFERENCES

1. Kirsner, J. B. Hormones and peptic ulcer; a review of clinical and experimental observations. To be published.
2. Metz, M. H. and Lackey, R. W. Treatment of peptic ulcer with posterior pituitary extract; preliminary report, *Tex. St. J. Med. 32*:589-90, 1937; and Peptic ulcer treated with the aid of posterior pituitary extract, *South. med. J. 36*:747-50, 1943.
3. Blotner, H. Gastric analyses and gastric symptoms in diabetes insipidus, *Amer. J. dig. Dis. 7*:73-75, 1940; and Personal communication, 1952.
4. Kobulnicky, E. and Bunyor, E. Die Ulkuskrankheit und das Hypophysen-Hypothalamus-System, *Schweiz. med. Wschr. 78*:832-33, 1948.
5. McGavack, T. H. Some endocrine factors concerned in the pathogenesis of peptic ulcer, *Med. Clin. N. Amer. 26:* 683-89, 1942.
6. Cushing, H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism), *Bull. Johns Hopkins Hosp. 1*:137-95, 1932.
   Comroe, B. J. Association of pituitary tumor and peptic ulcer, *Amer. J. med. Sci. 186*:568-73, 1933.
   Swan, W. G. A. and Stephenson, G. E. Basophil adenoma of the pituitary body; report of a case, *Lancet 1*:372-74, 1935.
   Vonderahe, A. R. Histopathologic changes in the nervous system in cases

of peptic ulcer, *Arch. Neurol. Psychiat. 41*:871-912, 1939.

Wilson, H. T., Olson, J. D. and Rivers, A. B. Pituitary tumors and peptic ulcers, *Rev. Gastroent. 13*:371-73, 1946.

Rasmussen, P. S. Pituitary tumor with gastric erosions, *Nord. med. 39*:1502-03, 1948.

7. Bailey, P. Personal communication.
8. Bastenie, P. A., Desneux, J. and Kowaleswski, K. Cliniques, physiopathologie et thérapeutique endocrino-gastroduodénales, *Acta gastro-ent. belg. 12*, Suppl.: 57-94, 1949.
9. Kirsner, J. B. and Sayman, W. Unpublished data.
10. Beattie, J. The relation of the tuber cinereum to gastric and cardiac functions, *Canad. med. Assoc. J. 26*:278, 1932.

Heslop, T. S. The nervous control of gastric secretion, *Brit. J. Surg. 25*: 884-99, 1938.

11. Winkelstein, A. Peptic ulcer in adolescence; its relation to pituitary dysfunction, *J. Mt. Sinai Hosp. 12*:773-75, 1945.
12. Brown, A. The influence of hyperthyroidism upon the secretion of free hydrochloric acid, *Ann. Surg. 92*:321-30, 1930.

Schwanke, W. Basedowsche Krankheit und Magensekretion, *Klin. Wschr. 14*: 1849-50, 1935.

Thiele, W. Störungen der Magenazidität bei der Hyperthyreose, *Dtsch. med. Wschr. 65*:1736-39, 1939.

Allende, M. The influence of hyperthyroidism and hypothyroidism in clinical and secretory functions of gastric juice, *Rev. Gastroent. 13*:303-05, 1946.

13. Brown, R. B., Pendergrass, E. P. and Burdick, E. D. The gastrointestinal tract in hyperthyroidism, *Surg. Gynec. Obstet. 73*:766-83, 1941.
14. Berryhill, W. R. and Williams, H. A. Study of gastric secretion in hyperthyroidism before and after operation, *J. clin. Invest. 11*:753-60, 1932.
15. Wilkinson, S. A., Jr. Gastric acidity in thyroid dysfunction, *J. Amer. med. Assoc. 101*:2097-99, 1933.
16. Lerman, J. and Means, J. H. Gastric secretion in exophthalmic goitre and myxoedema, *J. clin. Invest. 11*:167-82, 1932.
17. Bastenie, P. A. and Kowalewski, K. P. Gastro-intestinal disturbances in insufficiency of the thyroid gland, *Gastroenterologia 74*:225-37, 1947.
18. Garbat, A. L. The simultaneous occurrence of active peptic ulcer and active hyperthyroidism, *J. Mt. Sinai Hosp. 17*:787-92, 1951.
19. Gill, A. M. and Walton, K. W. Hyperthyroidism and peptic ulcer, *Lancet 1:* 693-94, 1952.
20. Lerman, J., Ricketts, H. T. and Werner, S. C. Personal communications.
21. Grove, W. R. and Vines, H. W. C. Calcium deficiencies; their treatment by parathyroid, *Brit. med. J. 1*:791-95, 1922.
22. Alkan, L. La tétanie viscérale, *Arch. Mal. Appar. dig. 21*:813-20, 1931.

Palier, E.: L'origine endocrinienne de l'ulcère gastroduodénal et son traitement par l'extrait parathyroide, *Bull. gén. Thér. 177*:176-80, 1926.

Moutier, F. and Camus, L. Nouvelle recherches sur le traitement de l'ulcère gastroduodénal par l'extrait parathyroidiene, *Arch. Mal. Appar. dig. 21:* 834-48, 1931.

Cain, A. Sur le traitement de l'ulcère de l'estomac par l'hormone parathyroidienne, *Rev. crit. Path. Ther. 1*:285-88, 1930.

23. Crabb, J. A. Peptic ulcer, an endocrine disease, *J. Kans. med. Soc. 44*:368, 1943.
24. Levy, M. M. and Levy, E. Les resultats éloignes du traitement des ulcères gastro-duodéneaux par l'extrait parathyroidien, *Arch. Mal. Appar. dig. 21:* 916-36, 1931.
25. Kirsner, J. B., Levin, E. and Palmer, W. L. The effect of various hormonal preparations upon gastric secretion in patients with duodenal ulcer. To be published.
26. Howard, J. E., Reifenstein, E. C., Jr. and Sprague, R. Personal communications.
27. Steinberg, H. and Waldron, B. R. Idiopathic hypoparathyroidism; an an-

alysis of fifty-two cases, including the report of a new case, *Medicine 31:* 133-54, 1952.

28. Rogers, H. M., Keating, F. R., Jr. Morlock, C. G. and Barker, N. W. Primary hypertrophy and hyperplasia of the parathyroid glands associated with duodenal ulcer, *Arch. intern. Med. 29:*307-21, 1947.
29. Läuchli, P. Hyperparathyreoidismus and Gastroduodenalulcus, *Schweiz. med. Wschr. 80:*1332-35, 1950.
30. Robinson, A. W., Black, B. M., Sprague, R. G. and Tillisch, J. H. Hyperparathyroidism due to diffuse primary hyperplasia and hypertrophy of the parathyroid glands; report of case, *Proc. Mayo Clin. 26:*441-46, 1951.
31. Burnett, C. H., Commons, R. R., Albright, F. and Howard, J. E. Hypercalcemia without hypercalcuria, calcinosis and renal insufficiency, *New Engl. J. Med. 240:*787-98, 1949.
32. Kirsner, J. B. Electrolyte disturbances in peptic ulcer, in *Peptic ulcer* (Sandweiss, D. J., editor), Philadelphia, W. B. Saunders Co., 1951, chapt. 62.
33. Colwell, A., Conn, J. W., Levine, R. and Ricketts, H. T. Personal communications.
34. Marble, A. Diabetes mellitus, in *Oxford medicine,* New York, Oxford Univ. Press, 1951, v. 4, pp. 131-178.
35. Joslin, E. P. *The treatment of diabetes mellitus.* 6.ed. Philadelphia, Lea & Febiger, 1937.
36. Wilder, R. M. *Clinical diabetes and hyperinsulinism.* Philadelphia, W. B. Saunders Co., 1940.
37. Wood, M. N. Chronic peptic ulcer in ninety-four diabetics, *Amer. J. dig. Dis. 14:*1-11, 1947.
38. Bowen, B. D. and Aaron, A. H. Gastric secretion in diabetes mellitus, *Arch. intern. Med. 37:*674-84, 1926.
    Rabinowitch, I. M., Fowler, A. F. and Watson, B. A. Gastric acidity in diabetes mellitus; its clinical significance based on a study of one hundred cases, *Arch. intern. Med. 47:*384-90, 1931.
39. Feissly, R. Ulcère gastrique à répétition traité par insuline, *Arch. Mal. Appar. dig. 16:*325-28, 1926.
    Simnitzky, S. S. Das Insulin in der Therapie der peptischen Magengeschwüre, *Wien klin. Wschr. 40:*1635-37, 1927.
    Cade, A. and Barral, R. I. L'insulinothérapie dans les ulcères gastroduodénaux, *J. Med. franç. 24:*94-97, 1935.
    Jones, C. R. Insulin in the treatment of peptic ulcer, *Amer. J. dig. Dis. 1:* 135-36, 1934.
    Sperber, P. Insulin therapy for duodenal and peptic ulcer, *Rev. Gastroent. 3:*320-27, 1936.
    Roller, M. Insulinbehandlung von Ulkus und Gastritis in der Allgemeinpraxis, *Med. Klinik. 36:*803, 1940.
40. DeMole, M. Les traitements de l'ulcère gastro-duodénal par les hormones, *Gastroenterologia 69:*31-56, 1944.
41. Winkelstein, A. and Hess, M. Effect of insulin hypoglycemia on gastric secretion in duodenal ulcer and controls, *Gastroenterology 11:*326-36, 1948.
42. Abrahamson, E. M. Hyperinsulin as a factor in peptic ulcer, *Amer. J. dig. Dis. 12:*379-82, 1945.
43. Crain, E. L., Jr. and Thorn, G. W. Functioning pancreatic islet cell adenomas, *Medicine 28:*427-47, 1949.
44. Janowitz, H. D. and Crohn, B. B. Hyperinsulinism and duodenal ulcer, *Gastroenterology 17:*578-80, 1951.
45. Edkins, J. S. The chemical mechanism of gastric secretion, *J. Physiol. 34:*133-44, 1906.
46. Uvnäs, B. Digestive tract hormones, *Nord med. 27:*1645-49, 1945.
47. Woodward, E. R., Bigelow, R. R. and Dragstedt, L. R. Quantitative study of effect of antrum resection on gastric function in Pavlov pouch dogs, *Proc. Soc. exp. Biol. Med. 68:*473-74, 1948.
    Dragstedt, L. R., Oberhelman, H. A., Jr. and Smith, C. A. Experimental hyperfunction of gastric antrum with ulcer formation, *Ann. Surg. 134:*332-45, 1951.
48. Kirsner, J. B., Levin, E. and Palmer, W. L. Observations on the excessive nocturnal gastric secretion in patients with duodenal ulcer, *Gastroenterology 11:*598-617, 1948.
49. Kosaka, T. and Lim, R. K. S. Demon-

stration of the humoral agent in fat inhibition of gastric secretion, *Proc. Soc. exp. Biol. Med. 27*:890-91, 1930.

Gray, J. S., Bradley, W. B. and Ivy, A. C. On preparation and biological assay of enterogastrone, *Amer. J. Physiol. 118*:463-76, 1937.

50. Kirsner, J. B., Levin, E. and Palmer, W. L. Studies on nocturnal and 24-hour gastric secretion during the injection of an enterogastrone concentrate in man, *Gastroenterology 10*:256-73, 1948.
51. Ferayorni, R. R., Code, C. F. and Morlock, C. G. The effect of enterogastrone concentrates on gastric secretion in human beings, *Gastroenterology 11*:730-39, 1948.
52. Segal, H. L., Ellis, E. E. and Watson, J. S., Jr. Observations on the gastric secretion in two duodenal ulcer patients during prolonged injections of an enterogastrone concentrate, *Gastroenterology 15*:118-24, 1950.
53. Ivy, A. C. The prevention of recurrence of "peptic" ulcer: an experimental study, *Gastroenterology 3*:443-49, 1944.

Ivy, A. C., Littman, A. and Grossman, M. I. Recurrence of peptic ulcer in man as affected by treatment with an enterogastrone preparation, *Gastroenterology 12*:445-52, 1949.

54. Pollard, H. M., Block, M., Bachrach, W. H. and Mason, J. Treatment of peptic ulcer with enterogastrone, *Arch. Surg. 56*:372-85, 1948.

Sandweiss, D. J., Sugarman, M. H. and Lockwood, B. C. Enterogastrone in the treatment of patients with duodenal ulcer, *J. Amer. med. Assoc. 138*: 552-57, 1948.

55. Gambill, E. E., Morlock, C. G., Butt, H. R. and Wollaegar, E. E. Study of the effect of an orally administered enterogastrone preparation on the clinical course of patients with duodenal ulcer, *Gastroenterology 14*:228-34, 1950.

Bone, F. C., Cassel, C., Ruffin, J. M. and Reeves, R. J. Enterogastrone parenterally in the treatment of peptic ulcer: a controlled clinical study, *Gastroenterology 17*:35-38, 1951.

56. Okada, S. and Doi, T. Sur une nouvelle méthode de traitement de l'ulcère de l'estomac et du duodénum, *Arch. Mal. Appar. dig. 28*:935-48, 1938.
57. Schmassman, H. Zur Therapie des Ulcus ventriculi und des Ulcus duodeni; klinische Erfahrungen Robaden, 1944-1950, *Schweiz med. Wschr. 81*: 166-72, 1951.
58. Roulet, P. Versuche über experimentelle Magengeschwüre und deren Behandlung, *Schweiz med. Wschr. 75*: 912-13, 1945.
59. Hubacher, O. Peptic ulcer treated with gastric and intestinal extracts, *Lancet 2*:272-74, 1946.
60. Bubb, W. Erfahrungen bei der Behandlung der Ulcus-Krankheit, *Schweiz med. Wschr. 79*:663-68, 1949.
61. Burghartz, N. Dreijährige Erfahrung in der Behandlung mit Robaden bei 277 Ulcuskranken, *Ärtzl. Wschr. 6*: 509-12, 1951.
62. Barfred, A. Gastric and duodenal ulcers treated with Robaden, *Nord. med. 43*:748-53, 1950.
63. Stolte, J. B. Therapeutic experiment in peptic ulcer, *Lancet 2*:858-59, 1950.
64. Gray, J. S. Wieczorowski, E. and Ivy, A. C. Inhibition of gastric secretion by extracts of normal male urine, *Science 89*:489-90, 1939.

Gray, J. S. Present status of urogastrone, *Amer. J. dig. Dis. 8*:365-66, 1941.

65. Sandweiss, D. J. Enterogastrone, anthelone, and urogastrone, *Gastroenterology 5*:404-15, 1945.
66. Gray, J. S., Wieczorowski, E. and Ivy, A. C. Inhibition of gastric secretion in man with urogastrone, *Amer. J. dig. Dis. 7*:513-15, 1940.
67. Sandweiss, D. J., Sugarman, M. H., Friedman, M. H. F., Saltzstein, H. C. and Farbman, A. A. Effect of urine extracts on peptic ulcer; an experimental and clinical study, *Amer. J. dig. Dis. 8*:371-82, 1941.
68. Marañon, G., Sala, P. and Arguelles, G. Digestive symptoms in chronic suprarenal insufficiency (Addison's disease), *Endocrinology 18*:497-504, 1934.
69. Turner, F. P. Peptic ulcer and the pituitary adrenal system, *J. Maine*

med. Assoc. 42:170-73, 1951.

70. Sorkin, S. Z. Addison's disease, *Medicine 28*:371-425, 1949.
71. Rowntree, L. G. and Snell, A. M. *A clinical study of Addison's disease.* Philadelphia, W. B. Saunders Co., 1931.
72. Soffer, L. J. *Diseases of the adrenals.* Philadelphia, Lea & Febiger, 1946; and Personal communication.
73. Köhler, V. Nebennierenrindenhormon und Ulkuskrankheit, *Endokrinologie 26*:34-43, 1949.
    Reinhold, E. Mitteilung über Erfahrungen in der Nebennierenrindenhormonbehandlung des Ulcus ventriculi et duodeni, *Med. Klinik 39*:616, 1943.
74. Gunther, L. Clinical note on the use of desoxycorticosterone acetate in the treatment of duodenal ulcer, *U. S. Nav. med. Bull. 46*:1743-75, 1946.
75. Korbasch, R. Zur Therapie des Magengeschwürs mit Progesteron und anderen Cholesteron-Abkömmlingen, *Dtsch. med. Wschr. 68*:417, 1942.
76. Kapp, H. Zur Therapie des Ulcus ventriculi et duodeni, *Gastroenterologia 71*:283-88, 1946.
77. Bock, H. E. and Meinrenken, H. Grenzen der Nebennierenrindenhormonbehandlung der Magen-und Zwölffingerdarmgeschwür, *Dtsch. med. Wschr. 72*:149-53, 1947.
78. Biro, L. and Navy, G. Beziehungen zwischen Ulkuskrankheit und Nebenniere, *Gastroenterologia 76*:169-94, 1950-1951.
79. Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H. and Reifenstein, E. C., Jr. Colorimetric assay of 17-ketosteroids in urine, *J. clin. Endocrin. 1*:234-56, 1941.
80. de Muro, P. and Ficari, A. Adrenal glands and the gastrointestinal tract, *Rev. Gastroent. 14*:860-68, 1947.
81. Allodi, A. and Cionini, A. Studi sulla fisopatologia dell'ormone della fortecia surrenale; azione esercitata sulla secrezione gastrica, *Minerva med. 2*:449-53, 1936.
    Roholm, K. Clinical investigations into the effect of intravenous injection of insulin; action of adrenalin upon the stomach secretions, *Acta med. scand. 74*:359-69, 1931.
82. Sandweiss, D. J., Saltzstein, H. C., Scheinberg, S. R. and Parks, A. Hormone studies in peptic ulcer, *J. Amer. med. Assoc. 144*:1436-52, 1950.
83. Turner, F. P. Eosinophile responses to epinephrine and ACTH in peptic ulcer, *Gastroenterology 18*:419-26, 1951.
84. Best, W. R., Muehncke, R. C. and Kark, R. M. Studies on adrenocortical eosinopenia; a clinical and statistical evaluation of four-hour eosinophil response tests, *J. clin. Invest. 31*:733-42, 1952.
85. Kirsner, J. B. Unpublished data.
86. Gray, S. J., Benson, J. A., Jr., Spiro, H. M. and Reifenstein, R. W. Effects of ACTH and cortisone upon the stomach; its significance in the normal and in peptic ulcer, *Gastroenterology 19*:658-73, 1951.
    Gray, S. J., Benson, J. A., Jr., Reinfenstein, R. W. and Spiro, H. M. Chronic stress and peptic ulcer; effect of corticotropin (ACTH) and cortisone on gastric secretion, *J. Amer. med. Assoc. 147*:1529-37, 1951.
87. Kirsner, J. B., Klotz, A. P. and Palmer, W. L. Unfavorable course of gastric ulcer during administration of ACTH and cortisone, *Gastroenterology 20*:27-29, 1952.
88. Mirsky, I. A., Block, S., Osher, S. and Broh-Kahn, R. H. Uropepsin excretion by man; source, properties and assay of uropepsin, *J. clin. Invest. 27*:818-24, 1948.
89. Kirsner, J. B. and Palmer, W. L. Effect of corticotropin (ACTH) in chronic ulcerative colitis, *J. Amer. med. Assoc. 147*:541-49, 1951.
90. Habif, D. V., Hare, C. C. and Glaser, G. H. Perforated duodenal ulcer after ACTH therapy, *J. Amer. med. Assoc. 144*:996, 1950.
    Smyth, G. A. Activation of peptic ulcer during pituitary adrenocorticotropic hormone therapy, *J. Amer. med. Assoc. 145*:474-77, 1951.
    Sloan, S., Briggs, J. D. and Halsted, J. A. ACTH therapy for ulcerative colitis complicated by perforation of coexisting peptic ulcer, *Gastroenterol-*

*ogy 18:*438-42, 1951.

Moe, A. E. Gastric ulcer appearing during cortisone administration, *Gastroenterology 20:*343-47, 1952.

Davis, T. A. and Zeller, M. Multiple peptic ulcers with massive hemorrhage during oral cortisone therapy, *J. Amer. med. Assoc. 150:*31, 1952.

91. Selye, H. The general adaptation syndrome and peptic ulcer, in *Peptic ulcer* (Sandweiss, D. J., editor), Philadelphia, W. B. Saunders Co., 1951, chapt. 12.
92. Wilkins, L. and Levine, R. Personal communications.
93. Fordyce, A. D. and Evans, W. H. Suprarenal virilism, *Quart. J. Med. 22:* 557-66, 1929.

Broster, L. R. The adrenogenital syndrome, *Lancet 226:*830-34, 1934.

Haymaker, W. and Anderson, E. The syndrome arising from hyperfunction of the adrenal cortex; the adrenogenital and Cushing's syndrome—review, *New int. Clin. 4:*244-99, 1938.

Kepler, E. J. and Keating, F. R. Diseases of the adrenal glands; tumors of the adrenal cortex, diseases of the adrenal medulla and allied disturbances, *Arch. intern. Med. 68:*1010-36, 1941.

Albright, F. Cushing's syndrome; its pathologic physiology; its relationship to the adreno-genital syndrome and its connection with the problem of the reaction of the body to injurious agents, *Harvey Lect. 38:*123-86, 1942-1943.

94. Zubiran, J. M., Kark, A. E., Montalbetti, J. A., Morel, C. J. L. and Dragstedt, L. R. Peptic ulcer and the adrenal stress syndrome. To be published.
95. Theile, P. Beitrag zur Kenntnis der Geschwürsbildungen des Magens und Duodenum im Kindesalter, *Dtsch. Z. Chir. 150:*275-80, 1919.
96. Saltzstein, H. C., Farbman, A. A. and Sandweiss, D. J. Sex incidence of peptic ulcer in children, *Endocrinology 27:* 400-02, 1940.
97. Necheles, H., Bralow, S. P. and Scheinberg, S. Sex distribution of peptic ulcer in children, in *Abraham Levinson anniversary volume: Studies in pediatrics and medical history.* New York, Froben Press, Inc., 1949, pp. 211-213.
98. Hutter, K. Jahreszeitliche Schwankungen beim Magen-und Zwölffingerdarmgeschwür, *Arch. klin. Chir. 151:*651-700, 1928.
99. Tidy, H. The incidence of peptic ulcer at St. Thomas' Hospital, 1910-1937, *Brit. med. J. 1:*319-24, 1945.
100. Ivy, A. C. The problem of peptic ulcer, *J. Amer. med. Assoc. 132:*1053-59, 1946.
101. White, F. W. The incidence of gastroduodenal ulcer in *Peptic ulcer* (Sandweiss, D. J., editor), Philadelphia, W. Saunders Co., 1951, chapt. 18.
102. Ivy, A. C. and Martin C. G. Sex as a constitutional factor for susceptibility to peptic ulcer, *Gastroenterology 13:* 215-21, 1949.
103. Collins, S. D., Phillips, F. R. and Oliver, D. S. Disabling illness from specific causes among males and females of various ages, *Publ. Hlth Rep. 66:*1649-71, 1951.
104. Hess, L., and Faltitschek, J. Studien über Motilität und Sekretion des Magens; die Functionen des Magens intra menses, *Wien. klin. Wschr. 37:*427-29, 1925.
105. Van Zant, F. R. and Alvarez, W. C. What is the value of the gastric analysis? A study of the daily variations in the gastric acidity of two normal persons, *Proc. Mayo Clin. 6:*419-22, 1931.
106. Hellebrandt, F. A. and Brogdon, E. Validity of fractional gastric analysis, *Amer. J. dig. Dis. 2:*402-08, 1935.
107. Anderodias, J. L'ulcère de l'estomac dans ses rapports avec la grossesse et l'accouchement, *Rev. mens. Gynec. 6:*201-30, 1911.
108. Szenes, A. Ueber den Einfluss der Schwangerschaft, der Menstruation und des Klimakterium auf das Magen-und Duodenalgeschwür, *Mitt. Grenzgeb. Med. Chir. 37:*652-91, 1923-1924.
109. Mussey, R. D. Operations of necessity during pregnancy, *Proc. Mayo Clin. 2:*156, 1927.

110. Hurst, A. F. and Stewart, M. J. *Gastric and duodenal ulcer.* New York, Oxford Univ. Press, 1929.
111. Jones, F. A. Haematemesis and melaena, *Brit. med. J. 2*:441-77, 1947.
112. Winkelstein, A. Observations on ulcerations adjacent to experimental gastric pouches in dogs, *Amer. J. dig. Dis. 3*:229-31, 1936.
113. Sandweiss, D. J., Saltzstein, H. C. and Farbman, A. A. Relation of sex hormones to peptic ulcer, *Amer. J. dig. Dis. 6*:6-12, 1939.
114. Chavarri, M. A., Cervino, O. J. and Richieri, A. L'acción de extractos de urína de yegua preñada sobra la ûlcera gastroduodenal, *Prensa. med. argent. 37*:1729-33, 1950.
115. Muslow, K. W. and Brown, W. E. Peptic ulcer complicating pregnancy, *Amer. J. Obstet. Gynec. 31*:1041-43, 1936.
116. LeWinn, E. B. Peptic ulcer with hemorrhage during pregnancy and fetal death, *Amer. J. Obstet. Gynec. 54*:114-18, 1947.
117. Bernstine, J. B. and Friedman, M. H. F. Peptic ulcer in pregnancy, *Amer. J. Obstet. Gynec. 56*:973-76, 1948.
118. James, D. W. Peptic ulcer during pregnancy, with report of a case of perforation, *Brit med. J. 2*:74-75, 1948.
119. Bralow, S. P. Scheinberg, S. and Necheles, H. Peptic ulcer and pregnancy, *Amer. J. dig. Dis. 15*:137-41, 1948.
120. Nakai, T. On the gastric juice of pregnant women, *J. Biochem. Tokyo 5*:465-77, 1925.
121. Arzt, F. On the gastric juice during pregnancy, *Amer. J. Obstet. Gynec. 12*:879-83, 1926.
122. Strauss, M. B. and Castle, W. B. Studies of anemia in pregnancy; gastric secretion in pregnancy and the puerperium, *Amer. J. med. Sci. 184*: 655-62, 1932.
123. Labata, J. S. The effect of pregnancy on gastric secretion, *Amer. J. Obstet. Gynec. 38*:650-53, 1939.
124. Way, S. Relation between gastric acidity and the anterior-pituitary-like hormone content of urine in pregnant women, *Brit. med. J. 2*:182-89, 1945.
125. Venning, E. H. Adrenal function in pregnancy, *Endocrinology 39*:203-20, 1946.
Jailer, J. W. and Knowlton, A. I. Simulated adreno-cortical activity during pregnancy in an Addisonian patient, *J. clin. Invest. 29*:1430-36, 1950.
126. Borri, A. Über Magengeschwüre in Klimakterium, *Zbl. inn. Med. 25*:689-96, 1904.
127. Winkelstein, A. Possible relationship between the ductless glands secreting the sex hormones and peptic ulcer, *J. Mt. Sinai Hosp. 7*:29-31, 1940.
128. Albers, H. Magensalzsaüeresekretion nach Progynon, *Geburtsh. u. Frauenheilk. 2*:583-90, 1940.
129. Korbsch, R. Heilungen von Magenulzera durch Follikelhormon-Injektionen, *Dtsch. med. Wschr. 63*:599, 1937; and Über den Wirkungsmechanism der Keimdrüsenhormone beim Magengeschwür und bei der Gastritis, *Med. Klinik 38*:1114-15, 1942.
130. Parade, G. Die Bedeutung der Sexualhormone beim Ulcus pepticum, *Med. Klinik. 38*:1153; 1188, 1942.
131. Schulz, W. Die Behandlung der Ulzerationen am Magen-Darmtraktus mit weiblichen Sexualhormon, *Med. Klinik 35*:914-17, 1939.
132. Gülzow, M. Ulkus-und Gastritisbehandlung mit Sexualhormonen, *Dtsch. med. Wschr. 68*:1071-74, 1942.
133. Adams, C. Die Behandlung des Magen- und Zwölffingerdarmgeschwür mit Keimdrusenhormonen, *Gastroenterologia 66*:343-49, 1942.
134. Pastoriza, R. El benzoato de estradiol en el tratamiento de la ûlcera gastroduodenal, *Prensa med. argent. 31:* 1615-18, 1944.
135. Friedlaender, W. Tratamento de las ulceras gastricas y duodenales con hormonas sexuales femininas, *Arch urug. Med. 26*:144-52, 1945.
136 Albeaux-Fernet. Le traitement hormonal de l'ulcère digestif (abstract), *Presse méd. 54*:516, 1946.
137. Ojha, K. N. and Venkatachalan, K. Observations on the use of stilbestrol in the treatment of peptic ulcer, *Gas-*

*troenterology 18:*100-03, 1951.

138. Braunscheid, F. Ambulante Ulkusbehandlung mit Progynon per os, *Dtsch. med. Wschr. 68:*1048-50, 1942.
139. Walinski, K. Ueber die Hormonbehandlung des Magen-bzw. Zwölffingerdarmgeschwür, *Dtsch. med Wschr. 68:*817-18, 1942.
140. Roskam, J. and Delreé, G. Le traitement de l'ulcère gastrique et duodénal par les hormones sexuelles, *Bull. Acad. Roy. Belge. 8:*459-75, 1943.
141. Schittenhelm, A. Kritisches zur Hormontherapie, *Dtsch. med. Wschr. 68:* 1:33, 1942.
142. Abrahamson, R. H. and Hinton, J. W. Gastric mucosa as an endocrine gland, *Surg. Gynec. Obstet. 76:*147-63, 1943.
143. Meeroff, M. Hormonoterapia en la úlcera gastroduodenal, *Prensa med. argent. 37:*1738-44, 1950.
144. Schiff, L. and Felson, H. Effect of estrogenic hormone on gastric acidity, *Amer. J. dig. Dis. 5:*292-94, 1938.
145. Tangari, C. Prima indagini isotolgiche sul meccanismo di azione dell' ormone follicolare e della vitamina antiscorbutica sui processi ulcerosi dell mucosa gastrica umana, *Arch. ital. Anat. Istol. pat. 10:*309-19, 1939.
146. Sandweiss, D. J. The status of hormones in peptic ulcer therapy, in *Peptic ulcer* (Sandweiss, D. J., editor), Philadelphia, W. B. Saunders Co., 1951, chapt. 35.
147. Felson, H. and Schiff, L. Effect of anterior pituitary-like hormone on gastric acidity in man, *Amer. J. dig. Dis., 5:*777-78, 1938-39.
148. Tomenius, J. and Paulsen, F. On the relation between urogastrone and chorioniogonadotropin — the effect of chorionic gonadotropin upon gastric secretion, *Gastroenterology 18:*244-48, 1951.
149. Sandweiss, D. J. and Sugarman, M. H. Medical aspects of peptic ulcer, *Rev. Gastroent. 19:*271-85, 1952.
150. Page, R. C. and Heffner, R. R. Oral treatment of chronic duodenal and jejunal ulcer with an extract of pregnant mares' urine, *Gastroenterology 11:*842-47, 1948.
151. Kirsner, J. B., Levin, E. and Palmer, W. L. Failure of an extract of pregnant mares' urine to influence gastric secretion in man, *Proc Soc. exp. Biol. Med. 69:*108-11, 1948.

NOTICE

The Second Series of

MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

WILL BEGIN IN NOVEMBER 1953—DATES, SUBJECTS AND PANEL MEMBERS WILL BE ANNOUNCED LATER

EYE CHANGES IN RELATIONSHIP TO DISORDERS OF THYROID FUNCTION*

LAWRENCE W. SLOAN

Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University

EYE changes associated with disorders of thyroid function are seen both by thyroid clinicians and by ophthalmologists, but their points of view regarding them differ. The thyroid clinician looks upon such events as serious complications or casualties of treatment of the thyroid disorder for which he feels responsible although actually he may not be and thinks of them in terms of disturbed endocrine physiology; the ophthalmologist must consider them primarily as problems in therapy, sometimes immediate and urgent. The relationship between the thyroid disorder and the eye change must be subordinated at that point to the immediate problem of protecting the involved eye. In a casual or infrequent association with Graves' disease, the clinician is likely to be unimpressed by the problems of the eye changes because they will be encountered infrequently—for we must remember that a very large number of patients with toxic goiter never have noticeable eye changes regardless of changes in thyroid function; but to the thyroid clinician, who sees a large group of thyroid patients, and especially to the ophthalmologist, toward whom the patients with eye disorders gravitate, the problem is important and pressing. The fact that the incidence is low does not minimize in the least its seriousness. The surgeon is concerned over the development of hypothyroidism, recurrent nerve injury, and hypoparathyroidism, yet none of these complications is really comparable with severe ocular disfigurement, disability or loss of vision. It seems to me that so long as these threats exist the clinician handling disorders of thyroid function must do everything he can to avoid or prevent this complication, infrequent as it may be.

What *is* the actual incidence of these eye changes? Before answering this question, perhaps we should discuss what is meant by "eye changes" and present some facts regarding the type of thyroid disorder in which

* Presented at the Section on Ophthalmology of The New York Academy of Medicine, March 17, 1952. Manuscript received June 1952.

they occur. These eye changes have certain characteristics which I believe occur in association with no other disturbance. They are seen in patients who at some time or other suffer from Graves' disease. The goiter in this disease is a diffusely hyperplastic toxic gland. In our experience the condition is rarely, if ever, associated with toxic nodular goiter. Therefore, when eye changes are found associated with definite nodular goiter investigation should be conducted along other lines, especially if there is unilateral or asymmetrical exophthalmos. Usually exophthalmos is associated with perfectly definite evidence of hyperthyroidism and seems roughly in proportion to its degree of severity. Thus it is that one has come to be synonymous with the other in the general clinical view. But actually, although there is this close relationship between exophthalmos and hyperthyroidism, the two co-exist but not in any clear-cut *direct* cause-and-effect relationship. The physiological mechanism undoubtedly involves other structures, notably the pituitary, but this mechanism is not yet well understood and I shall concern myself with the clinical manifestations only.

The eye changes, as we look at the patients, are many and varied but we have come to think of them in general, as falling roughly into two categories, those with relatively simple disorders of the lid opening and closing mechanism in which the problem is largely cosmetic and seldom serious; and those which are serious because of infiltration of the orbital contents with edema and cells which ultimately may result in fibrous fixation of the globe. This may be complicated further by proptosis and "papilledema," so that the threat to normal eye function and possibly vision is considerable. Whether the mechanism of production of these two types of eye changes is fundamentally the same, I shall not consider at this time. There seems to be no sharp dividing line between the two, clinically, for we see those which show only mild lid spasm at one extreme, and extensive infiltration with severe spasm at the other. There are varying degrees of both in-between. I shall ask you to think of them respectively for the time being simply as "not severe" or "severe" so that we may get some idea of the incidence of the really severe eye changes which are the ones which incapacitate eye motion or threaten vision.

In a study of the results of the surgical treatment in 615 cases of toxic goiter made five years or longer after operation, there were twenty-one patients rendered euthyroid and one with persistent hyper-

thyroidism who were found to have had eye changes before operation that persisted or who developed eye changes after operation sufficiently conspicuous and important so that they were segregated for study. There were three in this group who would be classified as having *severe* eye changes, that is, who had some eye disability persisting five years or longer following thyroid operation. I believe that this reflects fairly accurately the incidence of severe eye changes following the surgical treatment of Graves' disease. It is about 0.5 per cent to 1 per cent. It is interesting and significant that at the time the study was made, all of the eye changes in this group had become stable. There was no loss of vision and plastic operations were performed on the lids and muscles of fourteen out of the twenty-two cases, largely for cosmetic reasons. The eye changes had become stationary in varying periods of time—from a few months to upwards of ten years.

Another group of 115 patients showing eye changes associated with thyroid disorders, treated during a ten year period, has been studied somewhat more carefully with respect to the fluctuations in thyroid function and these I shall attempt to summarize. This group does not include all the eye changes that occurred during that time but it does include very nearly all the severe ones from which we may again roughly estimate the incidence.

Of the 115 cases, fifteen have been classified as severe (see Tables I and II) which constitute an incidence of about 1 per cent of the total toxic goiter patients *treated*. By far the majority of these patients were treated by partial thyroidectomy for they occurred during the ten year period immediately preceding the introduction of thyroid-inhibiting drugs. Of the 115, all but nine were treated by partial thyroidectomy. Of these nine, seven received no specific thyroid treatment and two were given radiotherapy to the gland. One of the latter, a man aged fifty was the only patient in the group who required enucleation (of one eye). It seems to me that other features besides the age and sex of this patient are worth noting. His presenting symptoms were those related to his eyes, particularly tearing and fullness of the right eye for six weeks, with diplopia and a feeling of pressure over that eye. There was a soft fullness, the globe was described as "bluish" and there was chemosis and dilatation of the conjunctival vessels. His measurements were right eye 26, left 21.5, and he showed lagophthalmos. He had the signs and symptoms of only *slight* thyrotoxicosis and his B.M.R. was

SEVERE EYE CHANGES ASSOCIATED WITH CHANGES IN THYROID FUNCTION FOLLOWING SURGERY AND RADIOTHERAPY

TABLE I—MEN

	Eye Changes at Onset of Treatment		*Clinical Estimate of Thyroid Function Before Treatment*	*RX.*	*Eye Changes During and After RX. of Thyroid*	*Eye Result After RX. of Thyroid*
	Age	*Degree*				
1. L.F.	18	R=L*	Normal - mild (plus 5%)	Op.	Eyes worse as BMR fell R>L.	5 yrs.: worse than before operation and L>R (Euthyroid) 7 yrs.: eyes (prominent) R=L stationary (Euthyroid).
2. L.L.	39	R=L	Moderate (plus 56%)	Op.	Right eye became worse and severe as BMR fell (−28%)	5 yrs.: rt. eye severe (Euthyroid). 8 yrs.: eyes seemed *normal* (Euthyroid).
3. D.H.	40	R>L*	Mild (plus 20%)	Op.	Eyes worse as BMR fell.	5 yrs.: stationary without disability. (Euthyroid). 19 yrs.: unchanged (Euthyroid).
4. J.R.	43	R=L*	Mild (plus 18%)	Op.	Eyes much worse as BMR fell.	5 yrs.: stationary. Improved with plastic lid operations (Euthyroid). 11 yrs.: unchanged (Euthyroid).
5. J.M.	49	R=L*	Moderate (plus 57%)	Op.	Eyes worse as BMR fell. Very bad 4 to 5 mos. after operation.	2 yrs.: improved and stationary (Euthyroid). (Lid plastic operation done then with improvement). 4 yrs.: stationary (Euthyroid). Died 4 yrs. plus.
6. J.G.	50	R>L*	Mild (plus 31%)	X.	Rt. eye grew worse under x-ray Rx. without much change in thyroid function.	3 mos.: enucleation rt. eye (mild hyperthyroid). Lt. eye involved but less severely. 2 yrs.: lt. eye improved (Euthyroid). 7 yrs.: lt. eye slightly prominent—no disability (Euthyroid).

*—Showed increasing ocular disability the result of infiltrative or infiltrative combined with spastic changes.

X—X-ray.

SEVERE EYE CHANGES ASSOCIATED WITH CHANGES IN THYROID FUNCTION FOLLOWING SURGERY AND RADIOTHERAPY

TABLE II—WOMEN

Eye Changes at Onset of Treatment			*Clinical Estimate of Thyroid Function Before Treatment*	*RX.*	*Eye Changes During and After RX. of Thyroid*	*Eye Result After RX. of Thyroid*
	Age	*Degree*				
1. M.P.	24	R>L	Very mild (plus 6%)	Op.	Eyes worse as BMR fell.	1 yr.: worse than before Rx. (hypothyroid) 12 yrs.: eyes "normal" (euthyroid on thyroid)
2. E.F.	33	R=L*	Moderate (plus 39%)	Op.	Eyes worse as BMR fell.	14 mos.: stationary—severe (Euthyroid) 6 yrs.: stationary—severe (Euthyroid) (6 mos. pregnant).
3. M.W.	33	None*	Mild (plus 31%)	Op.	Severe bilat. infiltrative changes as BMR fell.	2 yrs.: stationary—severe (Euthyroid) No further follow-up.
4. G.S.	33	R>L*	Mild (plus 33%)	Op.	Unchanged—severe. Eyes prolapse.	12 yrs.: stationary—severe (Euthyroid) Eyes prolapsable.
5. M.D.	40	L>R*	Very mild (plus 15%)	X.	Rt. eye worse as BMR fell.	4 yrs.: rt. eye stationary—severe. (Euthyroid)
6. J.B.	42	None*	Mild (no record)	Op.	Eye worse as BMR fell.	3 yrs.: stationary—severe, R=L. (Euthyroid) Lost to follow-up.
7. E.H.	44	R=L*	Severe (plus 81%)	Op.	Eyes much worse as BMR fell.	9½ yrs.: stationary—seemed improved with thyroid and myomectomy (Euthyroid)
8. M.D.	47	R=L*	Moderate (plus 35%)	Op.	No change for 9 yrs then L>R.	9 yrs. 3 mos.: seemed improved with thyroid (Euthyroid) 24 yrs.: stationary *R>L* without symptoms (Euthyroid)
9. L.D.	55	R=L*	Mild (plus 68%)	Op.	Eyes worse after op. with corneal ulcer.	2 mos.: improved with bilateral plastic lid operations. 1 yr.: stationary—improved (Euthyroid) Lost to follow-up.

*—Showed increasing ocular disability the result of infiltrative or infiltrative combined with spastic changes.

X—X-ray.

plus 31 per cent. Following radiotherapy to the gland, the exophthalmos progressed on the right side and after exploration and partial orbital decompression and formation of lid adhesions, it was necessary to enucleate the right eye about three months after admission. Two years later he reported that he had seen no doctors during the preceding year, had simply applied cold compresses to the other eye three times a day, and that this eye was very much improved. He had no tremor or palpitation and had gained 15 pounds. I have almost come to the conclusion that this is the ideal form of therapy. In any event, time is a prime ingredient.

Two patients in this group, both women—aged thirty-three and forty-one respectively, had no eye signs or symptoms whatever prior to the institution of treatment for thyrotoxicosis. The thyroid disease was quite mild in both cases. On iodine and radiotherapy, the basal metabolism of the first fell to plus 18 per cent. She felt "a pressure" behind her eyes but no eye changes were noted. A month later her basal metabolism rose to plus 47 per cent and she was given iodine in preparation for operation. The metabolic rate fell to plus 27 per cent. The evidence for hyperthyroidism throughout (except the elevation of the B.M.R.) was largely subjective. After operation, the basal metabolism fell to plus 2 per cent and within a month of operation, her eyes were puffy, she complained of photophobia, and tearing. Four months later, she was euthyroid with a basal metabolism of plus 2 per cent but her eyes were very much worse—including limitation of rotation and spasm of the lid levators. Operation was suggested to protect the corneae but was refused. Four years later, the condition was somewhat improved and stationary. She was euthyroid (plus 2 per cent).

The course of the second case was very similar. She became moderately hypothyroid after operation during which interval her eyes grew worse. An unsuccessful plastic lid operation was performed on one eye two years after operation by which time the eyes seemed to have become stationary. They remained that way as long as she was followed (up to three years after operation) with definitely impaired function. She was euthyroid at that time (minus 9 per cent).

I should like to be able to present many other individual cases in detail, especially the more severe ones, because close study of these is far more instructive from a practical standpoint than a statistical analysis of such a complex subject. This is obviously impossible, however, and

I shall have to try to present the overall picture as well as I can by emphasizing what seem to be the significant features.

Let us look at the fifteen severe cases first. To recapitulate: All had toxic diffuse glands. Six of the fifteen were men. Of these, five were aged thirty-nine to fifty. The other was aged eighteen. Of the nine women, the ages were between thirty-three and fifty-five. Of all fifteen, ten were between the ages of twenty-nine and fifty-five.

An estimate of the thyroid function at the time the initial eye changes were noted reveals that nine were considered only mildly hyperthyroid, five were moderately toxic and one was severely toxic.

An estimate of thyroid function during and after treatment indicates that function became normal promptly in nine patients and remained so, and that mild hypothyroidism developed in two. In another, there was little apparent change, but this is the patient requiring enucleation. One patient, who seemed really normal before operation except for his eyes, became hyperthyroid a short time after operation but meantime his eyes grew alarmingly worse. He was given radiotherapy to the gland with very little effect. Sometime later, his thyroid function reverted to normal apparently spontaneously. His eyes remained bad and at five years, they were worse than before operation. At seven years, they were both still prominent but satisfactory, about equal, and causing no disability. He was euthyroid.

Of the eleven who became normal or hypothyroid after treatment, the eyes grew worse in a relatively short period of time in nine. In the other two, the eye changes did not develop for five and nine years respectively. One of these became hypothyroid after operation without any eye changes developing immediately. He slowly reverted to normal function without therapy and at five years his B.M.R. was plus 1 per cent. At that point, aged forty-four, he developed severe exophthalmos in the right eye with diplopia but three years later his eyes appeared normal and caused no disability. He was euthyroid. The second, a woman aged forty-seven, with moderate symmetrical exophthalmos became euthyroid after operation and remained so for nine years, then at age fifty-six developed marked prominence of the left eye without disability. Her B.M.R. at that time was plus 12 per cent although clinically she seemed somewhat hypothyroid. On thyroid she improved. Three months later her eyes appeared normal and remained so. Since that time we have seen one other patient in whom this sequence of

events was similar to that of the preceding cases. At age 37, this patient showed mild asymmetrical exophthalmos with hyperthyroidism (B.M.R. plus 45 per cent). Thyroidectomy was performed and she became euthyroid without any change in her eyes immediately post-operatively. Eleven years later at age forty-eight, while still euthyroid (plus 5 per cent) but very obese, she developed severe, acute, bilateral, alarming exophthalmos which responded rapidly to thyroid administration. (Her acute signs and symptoms have disappeared but tend to recur if she discontinues thyroid.)

It will be noted that thirteen of the fifteen patients with severe eye symptoms in this group showed evidence of infiltrative changes in the orbits by the presence of diplopia, limited motions of the globe, resistance to its attempted reduction, frequent evidence of peri-orbital edema and associated acute signs of conjunctival congestion. Eye symptoms were complained of at times even before the eye signs became apparent: a feeling of fullness or pressure behind or "on top of the eye ball," "visual discomfort," "pain in the eye," burning or smarting and lacrimation.

In the remainder of the 115 cases of eye disturbances studied, the changes were characterized by an absence of the signs and symptoms of infiltration seen so frequently in the severe group. The changes seemed rather to be disturbances of innervation of smooth muscle components of the lid opening and closing mechanism and there was a far greater tendency toward improvement of the eye condition as the hyperthyroidism came under control. Fifteen of these patients could be classified as normal in appearance and function after varying intervals of time from a month or two to ten years after operation (or other therapy), forty-two were definitely improved and thirty-nine were unchanged. (The cases that progressed under treatment were the ones included in the severe group.) The two groups have at least one thing in common; the eye changes tend to become stationary after varying periods of time whether they advance or regress, and a certain number of them do not change at all with fluctuations in thyroid function.

The seven patients who showed eye changes and who received *no* therapy affecting thyroid function, form rather an interesting group. These patients were sent, or presented themselves, to the clinic with eye changes which showed the simpler, less severe types. Five of these patients were either euthyroid at the time of the initial eye change or

had extremely mild and equivocal symptoms of hyperthyroidism but often a history of some kind of functional thyroid disorder. One of the patients was quite hypothyroid. One of the patients had a B.M.R. of plus 50 per cent but clinically the evidence of hyperthyroidism was not striking. In this patient, after a period of nine years, there was "spontaneous" remission to a frankly euthyroid state (minus 7 per cent). At eleven years, her eyes improved and appeared normal. She is one patient at least in whom we think there might have been an actual diminution of 3 mm. in the proptosis. There was unilateral exophthalmos in five of the seven patients. In the other two, it was bilateral and symmetrical. Initial studies were made to rule out other causes of unilateral exophthalmos. The subsequent courses, however, suggested quite strongly that these were of the thyroid type in four out of the five at least, because in three of them the eyes became normal, and in the fourth the eye which was exophthalmic initially, became normal and the other eye became prominent. In the fifth case, there was no change during a short follow-up interval. Of the two bilateral cases, one improved bilaterally and the other showed regression of one eye to normal, the other remaining prominent. The ages of these patients were twenty-eight to thirty-eight and all were women.

In some ways these patients resemble the three severe cases discussed earlier who had delayed eye changes at a time when they were euthyroid and had been so for many years. The patients with the delayed *severe* eye changes were all in the older age groups, however, and this may be of significance.

Out of this rather confusing mass of data, we set ourselves the task of trying to discover whether there were any clues which would be of help in spotting among those patients who came under our observation, any who might be expected to develop severe eye changes during or after treatment. One thing seemed quite certain: if such cases could be spotted, operation should be avoided if possible for we had found that the majority of the severe eye changes developed quite rapidly following partial thyroidectomy. This was interpreted as an abrupt and perhaps irreversible upset in the physiological balance which had maintained the various components of eye motion as nearly normal as possible under the abnormal conditions of hormone secretion in the thyroid, pituitary and possibly other glands. It was felt that the same result might be expected to occur following any form of therapy which acted

relatively rapidly and "irreversibly," as for example radioactive iodine. Realizing that the disease was self-limited, it followed that if the progression of the exophthalmos could be prevented and the eye protected during the often protracted period of change, the major problem might be solved and we might no longer have reason to fear this complication.

If then we further summarize and bring together those features of the data which I have attempted to present which seem to be pertinent, I think we do come up with some characteristics of this disorder significant enough clinically that are worth looking for in patients with definite or suspected Graves' disease.

1. *Age:* The majority of the patients who developed severe eye changes were between the ages of thirty-nine and fifty-five, that is *older* patients.

2. *Sex:* A higher proportion of men within that age group developed severe eye changes than develop Graves' disease as compared to women. Therefore look out for the older men with eye changes.

3. *Thyroid function at the time of initial eye change:* The majority of the cases were considered only mildly toxic or even normal and often remained so as the eye signs developed out of proportion to the *clinical* evidence of hyperthyroidism. This seemed to hold true even in patients whose basal metabolism tests were reported elevated. In other words, there seemed to be a tendency in general for the eye changes to develop early and out of proportion to the degree of hyperthyroidism which one usually associates with such severe exophthalmos. It is this group of patients who, because of the severe exophthalmos, may be operated upon inadvisably on the assumption that the exophthalmos is an expression of both the presence and the *degree* of hyperthyroidism.

4. Of the significant early signs and symptoms, lid-fullness, lacrimation, and a sense of fullness or pressure in the eye, at times with diplopia, seemed of particular importance. In asymmetries of the eyes it is most important to try to determine whether the asymmetry is due to infiltrative changes within the orbit (resistance to attempted reduction of the globe, occasional palpable lateral recti, examination of fields for diplopia) or due simply to "spastic" changes producing asymmetries of appearance with only mild, or even perhaps an absence of, exophthalmos.

Any one of these features by itself may prove misleading, for we find exceptions in everyone of these categories. But if we find combina-

tions of these various characteristics present as patterns in any given patient, the evidence grows that here we may be dealing with a potential case of "malignant exophthalmos" and we had better proceed slowly and cautiously in treating the hyperthyroidism.

The actual procedure carried out is, in general, to treat cases manifesting the above patterns with prolonged drug therapy cautiously administered if the hyperthyroidism is severe enough to warrant this. The dose of drug is altered with the changing condition of the eyes, being prepared to take measures at any point in the treatment necessary to protect them. When eye changes appear to be advancing, either the dose of the drug will be decreased or the patient will be given thyroid substance unless the hyperthyroidism is severe. The combination of severe hyperthyroidism and severe disabling exophthalmos is not very common but when it does occur it is the most difficult situation of all to control and a great threat to eye function. Occasionally there just is nothing which seems capable of arresting the relentless progress of the disease. Protection of the eyes becomes of paramount importance. It is with this small group of patients that the ophthalmologist and occasionally the neurosurgeon get their morbid impressions of the inadequacies of thyroid clinicians.

The role of administration of thyroid substance in the treatment of these patients is not clear. It is a difficult point to evaluate. It is still more a feeling than any actual evidence we have that thyroid substance helps. We have seen a number of patients, especially those with acute eye signs and symptoms, in whom there has been a fairly prompt response. This has been impressive enough so that we push thyroid in every possible case in which the eye changes appear to be progressive. But whether it is due to this, or to the caution in handling these patients, combined with the known tendency of the disease to be self-limited so that eventually the eyes become stabilized anyway, we are not certain. We do feel sure that in some of the *acute* cases the degree of proptosis is reduced (by actual careful measurements), but that the final degree of protrusion of the globe, once stability is restored, is seldom if ever less than at the beginning, and usually more even if only slightly so.

Furthermore, no one believes that there is anything specific about the action of the commonly used thyroid-inhibiting drugs in controlling exophthalmos. The important fact is that they permit a slow, reversible and controllable modification of thyroid function during the period

while the eye changes are taking place. This, it has seemed to us, has proved of considerable help in management of the eye problems for we know that the process is self-limited and that with time, patience, and careful following, the severe eye changes are not so likely to develop. Nevertheless, they have been reported in patients treated with radioactive iodine.

Whatever the virtues of one agent or method of treatment of Graves' disease as compared with another, and whatever the reasons for these associated eye changes, the internists, ophthalmologists and surgeons in our group are in essential agreement about the plan of management, based largely upon our experience with them, the main outlines of which I have attempted to delineate. We are agreed also that among the patients with Graves' disease whom we have treated during the past six years, there have been nowhere near the number of severe eye problems we saw in the groups which I have presented, and which represent our experience before the introduction of thyroid-inhibiting agents and radioactive iodine. This is not to imply that patients having this complication have not been seen by us during this interval. A fairly large number have been referred to the clinic or seen in consultation, but we have a dangerously optimistic feeling that fewer of them have been home-grown. Certainly, I can say for patients treated surgically that we have had fewer eye problems. I have a record of only one whose progressive and severe course I think we should have foreseen and forestalled during that time.

Probably the factor which is most important of all in avoiding eye trouble in Graves' disease is an *awareness* that it can and does occur (especially in patients showing any of the clinical patterns of eye changes and thyroid function I have tried to describe) so that in handling these patients we have become wary of any eye changes. We attempt to evaluate them and treat them with the cooperation and expert assistance of an ophthalmologist who follows the patients with examinations and accurate measurements throughout the course of thyroid treatment, intervening to protect the eye when indicated, whether the patient is being treated by drugs, radioactive iodine, surgery, or combinations of these methods.

After studying the individual patients in considerable detail and then the group as a whole, one comes to a point of view which may be summarized about as follows:

In Graves' disease, the train of events involving the eyes appears to be coincidental with the changes producing disturbances in thyroid function, although clinical evidence of the changes in the latter may be minimal or even lacking at the time the process begins. This train of events as it affects the eyes, however, *once started runs its course*, regardless of changes in thyroid function. Change in thyroid function produced by partial thyroidectomy, however, does appear to modify the course of these eye changes more frequently and more seriously than any other measure employed in altering thyroid function. This is most likely to occur when thyroidectomy is performed between the ages of forty to fifty-five, particularly in men. It seems likely that the stimuli which produce the thyroid change, also produce the eye change but each runs its almost independent course. In other words, changes in thyroid function from whatever form of therapy, or even "spontaneously" may modify the course of the eye changes but these appear to be quite definitely and more seriously modified or altered only by partial or subtotal thyroidectomy. Although difficult to prove, it is doubtful whether any other form of thyroid treatment so far employed actually does modify the natural course of this process.

FORTNIGHT SERIES IN BOOK FORM

The lecture series presented at the Graduate Fortnight of The New York Academy of Medicine have been published in book form and are on sale at The Macmillan Company, 60 Fifth Avenue, New York.

THE MUSCULOSKELETAL SYSTEM

Twenty-Third Annual Fortnight, 1950 . . . . . $6.50

DISORDERS OF THE CIRCULATORY SYSTEM

Twenty-Fourth Annual Fortnight, 1951 . . . . . $5.50

ON QUALIFICATIONS FOR SCHOOL MEDICAL DIRECTOR

Statement by The New York Academy of Medicine on New York City Board of Education Resolutions*

(Condensed Text)

A new plan for the selection of a chief for the medical division of the city's school system was adopted on October 2 of this year by the Board of Education. It contravenes recommendations for qualifications which The New York Academy of Medicine, upon invitation, had submitted as essential for superior medical service. Because of the importance of this medical post, the Academy is moved to speak out publicly in protest against the Board's action and to explain the basis of its objections. In this statement the Academy will also set forth its recommendations and the principles underlying them.

It is enlightening to review the long history of the subject, particularly the repeated requests for the Academy's advice and the repeated nullifications of its recommendations. In 1936, at the instance of the Superintendent of Schools, the Academy made a comprehensive study of the work of the Medical Division of the Board of Education, which resulted in recommendations for a reorganization of the Division to provide for adequate medical service with a well-qualified staff. The next year the Academy advised the Board of Examiners of the Board of Education as to the duties and qualifications of the professional staff of the Division and aided in obtaining qualified persons to conduct examinations for the positions.

In September 1940, the Academy's assistance was again sought, concerning the reorganization of the Medical Board, including the qualifications for the position of chief medical officer. Incidentally, the post has borne several different titles over the years.

In the midst of the Academy's deliberations, Dr. John E. Conboy, an ophthalmologist, was designated in February 1941, by the Board of Education as Acting Chief Medical Examiner. He had been an examining physician receiving an annual salary of $4,000 for part-time service.

After several months of study, the Academy recommended in June 1941, that the director of the Medical Division be a physician thoroughly versed in internal medicine, that he should be a man of forceful personality and that he should possess executive and organizing ability. It was recommended further that the preparation for this position should include:

1. An internship of at least 18 months on a straight medical or a mixed service; if on mixed service, at least six months should have been spent on the medical service.
2. At least one year of medical residency.
3. Five years' service on the visiting inpatient staff of an approved hospital.

The Academy advised, among other things, that the director should be appointed on a full-time basis, with the understanding that he should "hold a position on the inpatient service of an approved hospital."

Most of these recommendations were incorporated in the bylaws of the Board of Education as of March 25, 1942. The suggestion as to hospital service was, however, misconstrued, and the bylaws were worded

* Original prepared by a subcommittee of the Committee on Public Health Relations consisting of Asa L. Lincoln, M.D., Chairman, Linn J. Boyd, M.D., C. G. deGutiérrez-Mahoney, M.D., Harry S. Mustard, M.D., Howard A. Patterson, M.D., I. Ogden Woodruff, M.D., H. D. Kruse, M.D., Secretary. Original approved by Committee on Public Health Relations, November 24, 1952.
Original approved by Wm. Barclay Parsons, M.D., President, The New York Academy of Medicine, December 4, 1952.

to read that the Chief Medical Examiner be required "to render continuous, regular ward service as consultant internist in a public hospital of Grade A standing in the City of New York."

The inclusion of the word "continuous" made the provision completely unworkable. No physician could direct a staff of medical examiners in the school system and at the same time give "continuous ward service" in a hospital.

The Academy had, of course, no intention of suggesting continuous hospital service. The recommendation was meant to imply attendance at weekly staff meetings, possibly a teaching assignment once a week, and in addition ward service of one month or so annually, during which the official would spend not more than one or two hours a day on ward duty. It should be observed here that this suggested arrangement is not unusual.

Within a few months after the Board's amendment of its bylaws, the United States was drawn into the Second World War, with a consequent shortage of physicians. There was no attempt at this time to make a permanent appointment. In November 1942, however, the Board assigned the duties to Dr. Conboy on a provisional basis at an annual salary of $7,500 and granted him leave of absence without pay from his civil service position of examining physician. This status continued through the war.

With the war over and most physicians back in the community, the Academy again took up the question. Under the date of June 14, 1946, a letter was addressed to Mr. Andrew G. Clauson, Jr., who had just become president of the Board of Education, suggesting that the matter be brought up and settled as proposed by the Academy in its reports of 1940 and 1941.

Meanwhile the Municipal Civil Service Commission, under whose jurisdiction examinations for this position lay at that time, notified the Board of Education in April 1946 that it would be necessary to hold a competitive examination for the appointment. On May 14, 1946, the then Superintendent of Schools recommended to the Board that the bylaw adopted in 1942 be repealed, on the ground that, together with the examination, its requirements would eliminate the incumbent from the position he had held provisionally for four years, although provisional appointments were limited by law to a few months' duration. Accordingly, at a meeting on July 10, 1946, the Board repealed the bylaw setting forth the qualifications of the Chief Medical Examiner and thus abolished the position.

The next move was to return the incumbent, Dr. Conboy, to his former status of examining physician and assign him to be "in charge of the medical staff" at a salary of $7,500. Thus the requirement for examination by the Civil Service Commission was circumvented, the temporary appointee was placed on a permanent basis, and an eye specialist remained in charge of this heavy medical responsibility.

At this point the Civil Service Reform Association went into action. It brought suit to compel the Board of Education and the Municipal Civil Service Commission to fill the position in accordance with the law. In this proceeding The New York Academy of Medicine took part as amicus curiae.

The suit was lost in the lower courts, not on the merits of the case, but on the ground that the proceeding had not been instituted within the statutory time limit. An appeal to the Court of Appeals resulted, however, in a reversal on April 22, 1948.

The Academy's brief stated that no personal disparagement of the incumbent was intended, but insisted that the position called for the qualifications set forth in the repealed bylaw, that these qualifications were the due of the public as well as of the employees of the Board of Education, and that such talent and experience were readily available. The brief also pointed out that the unrealistic stipulation that the incumbent should "render continuous ward service in a Grade A hospital" could have been easily amended.

Long delays and measures adopted by the Board, which had the effect of postponing compliance with the court order, were open to the interpretation that the Board was determined to retain Dr. Conboy. In the spring of this year, however, four years after the Supreme Court decision, Dr. Conboy retired. Now at last it appeared that the Board was ready to hold an open competitive examination to find a qualified physician to be appointed permanently.

The duties of the position, as set forth

in the most recent statement, are as follows:

Under the supervision of the Associate Superintendent in Charge of Personnel,

1. to plan, direct and supervise the work of the Medical Staff of the Board of Education; to program hours of service of the members of the Medical Staff in terms of needs;
2. to evaluate medical reports for diagnosis and prognosis and to interpret them to school officials for appropriate administrative action;
3. to organize in-service courses; to prepare bulletins dealing with the improvement of teacher health;
4. to initiate surveys and studies on topics such as: causes of absence; sabbatical leaves in relation to teaching and supervision and administration of teaching personnel;
5. to assist the Board of Examiners in determining appropriate health standards for prospective teachers and supervisors;
6. to act as Chairman of the Medical Board of the Board of Education Retirement system;
7. to attend hearings in cases of teachers under consideration by the Superintendent of Schools for retirement;
8. to attend joint hearings of the medical staff of the Teachers' Retirement Board and the Division of Teacher Training and Personnel of the Board of Education.

The scope, variety and importance of these activities are evident. To state the matter in its simplest terms, the health and medical problems arising among forty thousand teachers are the concern of the Chief School Medical Inspector; hence, he has a complex task and carries heavy responsibility not only directly for the well-being of the individual teachers, but also indirectly for that of the children.

Again the Board turned to the Academy for an opinion on the qualifications of the much disputed post. A draft of a proposed new bylaw covering the position, this time called "Chief School Medical Inspector," was submitted.

The requirements as set down by the Board in February 1952 included the following:

"*Preparation:* Graduation from an approved medical school or medical college and the holding of a license to practice medicine in the State of New York and present registration thereunder, and the holding of a certificate from an American qualifying specialty Board or a fellowship in the American College of Physicians or the American College of Surgeons. The said preparation shall include or be supplemented by, twelve semester hours in approved and appropriate courses. . . ."

"*Experience:* Ten years of approved experience in the practice of medicine, and one of which shall have been an internship in a hospital approved by the American Medical Association; and said experience to include administrative or supervisory experience over a period of two years and experience over a period of five years in the procedures and management of professional personnel in a public school system."

In view of the fact that the duties of the position demand a broad competence in clinical medicine, the Academy has repeatedly advised that the appointee be a physician trained in internal medicine, not a specialist in some limited branch of medicine. In its comment on the new qualifications, therefore, the Academy reiterated that a physician qualified in the wide scope of internal medicine be appointed, and expressed the view that he "should be a diplomate of the American Board of Internal Medicine and that certification by any other board should not be considered" and further, that "fellowship in the American College of Surgeons is irrelevant."

With respect to the requirement for ten years of experience, the Academy considered this reasonable. It was pointed out, however, that the internship requirement should not be set at one year, because during the war internships were reduced to nine months. The Academy recommended further that the applicant should have had an internship in a hospital approved by the American Medical Association, and, in addition, a residency of such duration and kind as is required for certification by the American Board of Internal Medicine. This really was implied in the requirement that he be a diplomate of that Board.

The document submitted to the Academy last February contained no reference to full-time or part-time service. In its reply,

however, the Academy urged, as in the former recommendation, that the position be on a full-time basis, with salary sufficient to attract a competent physician.

The new qualifications proposed by the Board made no provision for affiliation with a hospital. In its recommendations of 1940 the Academy had stressed this arrangement, and in its opinion of 1952, it re-emphasized the point, but with a suggestion that the proposed appointment to a hospital staff be not a part of the qualifications for the position. It was suggested that the Board of Education or the Superintendent of Schools should specify the time to be allowed for a hospital affiliation. A suggested plan would include attendance at weekly staff meetings and possibly one undergraduate teaching assignment a week; in addition there might be ward service for about two hours a day for a month or so each year.

Early in October 1952 it was learned that the Board of Education had adopted resolutions on qualifications for the post of "School Medical Director," as it was newly titled. The Academy's recommendation concerning the certification by the Board of Internal Medicine was accepted, and the reference to the American College of Surgeons was eliminated. Residency was not added to the requirements. After apparently accepting the basic principles suggested by the Academy, the Board proceeded, however, to nullify the high standards by providing for a waiver of all preparation and experience, substituting for them "five years of experience as School Medical Inspector—Personnel in the public schools of the City of New York." This waiver would make it possible for any physician already in the department for five years, regardless of his preparation, to be appointed.

It was specifically provided in the resolutions adopted that the position be part-time. The explanation was made that a hospital affiliation would result in part-time service; this was, of course, not the intention, and would not have so proved in practice, if properly arranged.

Lastly, the change in title to "School Medical Director" would permit the appointment of anyone who could pass the examination. For, under the Board's rules governing the filling of a position in which the title "director" appears, any eligible person who passes an examination may be appointed without regard to his standing. Thus a favored candidate might come last on a list and still receive the appointment.

From this account it may be seen that the recent action of the Board follows the familiar pattern. The Academy of Medicine submits that the long series of maneuvers by the Board of Education do not inspire confidence that the highest standards will prevail in the selection of a Chief School Medical Inspector. Moreover, the explanation by the Superintendent of Schools for the steps just taken may unfortunately convey the impression that the qualifications adopted by the Board conform substantially to the recommendations of the Academy, and therefore carry its approval. Actually, while seeming to subscribe to the Academy's recommendations, the Board's resolutions through exceptions permit them in effect to be nullified. And far from giving blanket endorsement to the Board's set of qualifications, the Academy is opposed to those portions dealing with part-time, substitution for clinical preparation and experience, and change of title, all of which tend to lower the standards.

Representatives of the Academy of Medicine conferred with the President of the Board of Education, and the Superintendent of Schools to discuss and clarify the divergent views of the two organizations. Agreement on the three points at issue was not reached.

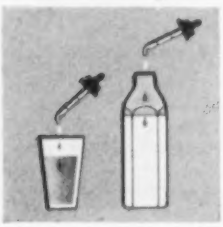
It should be noted well that the qualifications for the Chief School Medical Inspector have their ultimate influence on the health of the children in this city. The Academy is bringing to public attention the long record of the Board of Education in this matter, including its latest action, because it believes that the interests of the people, the teachers, and above all the children, are not being fully safeguarded.

To summarize, the Academy is opposed to those parts of the qualifications for the Chief Medical Officer set by the Board which do not meet the high standards which the Academy has repeatedly recommended, and the Academy calls for the adoption of qualifications which will insure the best medical service for the teachers without nullifying exceptions.

superior flavor

Pleasant-tasting. No disagreeable aftertaste. Readily accepted without coaxing.

on every count



superior miscibility

Disperse readily in formula, fruit juice or water. Mix well with cereals, puddings or strained fruits.

superior convenience

Light, clear and non-sticky. Can be accurately measured and easily administered. No mixing necessary.

superior vitamin supplements for infants...

superior stability

Require no refrigeration. May safely be autoclaved with the formula.

Poly-Vi-Sol

MEAD

MEAD JOHNSON & COMPANY

Evansville 21, Ind., U.S.A.

	Vitamin A	Vitamin D	Ascorbic Acid	Thiamine	Riboflavin	Niacinamide
POLY-VI-SOL Each 0.6 cc. supplies	5000 units	1000 units	50 mg.	1 mg.	0.8 mg.	6 mg.
TRI-VI-SOL Each 0.6 cc. supplies	5000 units	1000 units	50 mg.			
CE-VI-SOL Each 0.5 cc. supplies			50 mg.			

All vitamins are in synthetic (hypoallergenic) form.

Fig. 1: "Roentgen examination . . . revealed the ulcer to be very much in evidence."

Fig. 2: In ten weeks "the ulcer niche was no longer in evidence roentgenologically or gastroscopically."

Clinical Evaluation of Pro-Banthine*

CASE REPORT

"M. D., female, aged 48, had a posterior gastrojejunostomy 14 years ago for duodenal ulcer. The patient was fairly well until nine months ago when severe, intractable pains occurred. She was hospitalized and a subtotal gastrectomy was done.

"She remained well for only a few months and was referred to us because of recurrence of very severe pain and marked weight loss. Roentgen study revealed a fairly large ulcer niche on the gastric side of the anastomosis.

"The patient had been on various types of antacids and sedatives without relief from pain. She was given 60 mg. of Pro-Banthine q.i.d. and within 72 hours was able to sleep through the night for the first time in weeks.

"At the end of two weeks of such treatment the patient had absolutely no pain and felt that she had been 'cured.' Roentgen examination at this time revealed the ulcer to be very much in evidence (*Fig. 1*). Much persuasion was necessary to make the patient realize the importance of maintaining her diet and therapy.

"Ten weeks of controlled regulation was necessary before we were satisfied that the ulcer niche was no longer in evidence roentgenologically or gastroscopically (*Fig. 2*).

"She has been maintained on 30 mg. [q.i.d.] of Pro-Banthine for almost five months with no recurrence of symptoms."

Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, to be published.

Pro-Banthine (*brand of propantheline bromide*), the new, improved anticholinergic agent, is more potent and, consequently, a smaller dosage is required and side effects are greatly reduced or absent.

Peptic ulcer, gastritis, intestinal hypermotility, pancreatitis, genitourinary spasm and hyperhidrosis respond effectively to Pro-Banthine, orally, combined with dietary regulation and mental relaxation.

*Trademark of G. D. Searle & Co.

SEARLE *Research in the Service of Medicine*

PROTECTED...

from the discomfort of allergy for a whole day

'Perazil'® brand *Chlorcyclizine Hydrochloride,*
50 mg., Compressed, scored

One 'Perazil' 50 mg. usually gives comfort for 12 to 24 hours.

Histamine antagonist, notable for its relative freedom from side effects

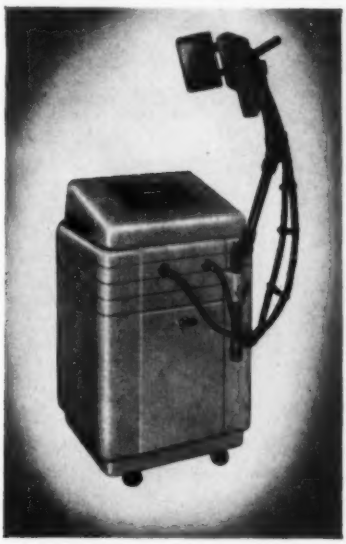
Supplied: In bottles of 100 and 500.

BURROUGHS WELLCOME & CO. (U. S. A.) Inc., *Tuckahoe 7, N. Y.*

COMPLETELY MODERN...

HANOVIA MEDICAL DIATHERMY

ALL DIATHERMIES MUST BE APPROVED BY THE F C C
BY JULY 1. REPLACE YOUR OLD MACHINE NOW



Everything necessary and desirable in the practice of advanced diathermy can be found in this one superbly designed instrument. Hanovia's engineers have created a unit that utilizes any of the approved types of applicators including air-spaced, electro induction cable, drums or special drum applicator and cuff electrodes. Also equipped for minor surgery, the Hanovia diathermy offers doctors and hospitals an unsurpassed versatility.

- FLEXIBLE IN APPLICATION
- NEW EASE OF OPERATION
- FINGERTIP CONTROL
- HEAVY DUTY PERFORMANCE
- FCC APPROVED
- A.M.A. COUNCIL ACCEPTED

Send for detailed literature NOW. Write Dept. BNY-6-53

HANOVIA
CHEMICAL & MFG. COMPANY
Newark 5, New Jersey

for your
peptic ulcer
patients...

Antrenyl™
bromide

OXYPHENONIUM BROMIDE CIBA

New High Potency
Anticholingeric with
No Bitter Aftertaste

As adjunctive therapy in your standard peptic ulcer regimen*, Antrenyl offers potent anticholinergic action to inhibit motility of the gastrointestinal tract and gastric secretion.

Although Antrenyl is one of the most potent of all anticholinergic agents, it rarely causes esophageal or gastric irritation and has no bitter aftertaste. In individualized doses, it is well tolerated and side effects are absent or generally mild.

In one study[1] patients receiving Antrenyl obtained relief from acute symptoms within 24 to 36 hours. Dosage was individually adjusted at 5 to 10 mg. four times a day. Side effects were adjudged less pronounced than those of other similar agents ordinarily used in the management of peptic ulcer.

Prescribe Antrenyl in your next case of peptic ulcer and spasm of the gastrointestinal tract. Available as tablets, 5 mg., scored, bottles of 100; and syrup, 5 mg. per teaspoonful (4 cc.), bottles of 1 pint.

Ciba Pharmaceutical Products, Inc., Summit, N. J.

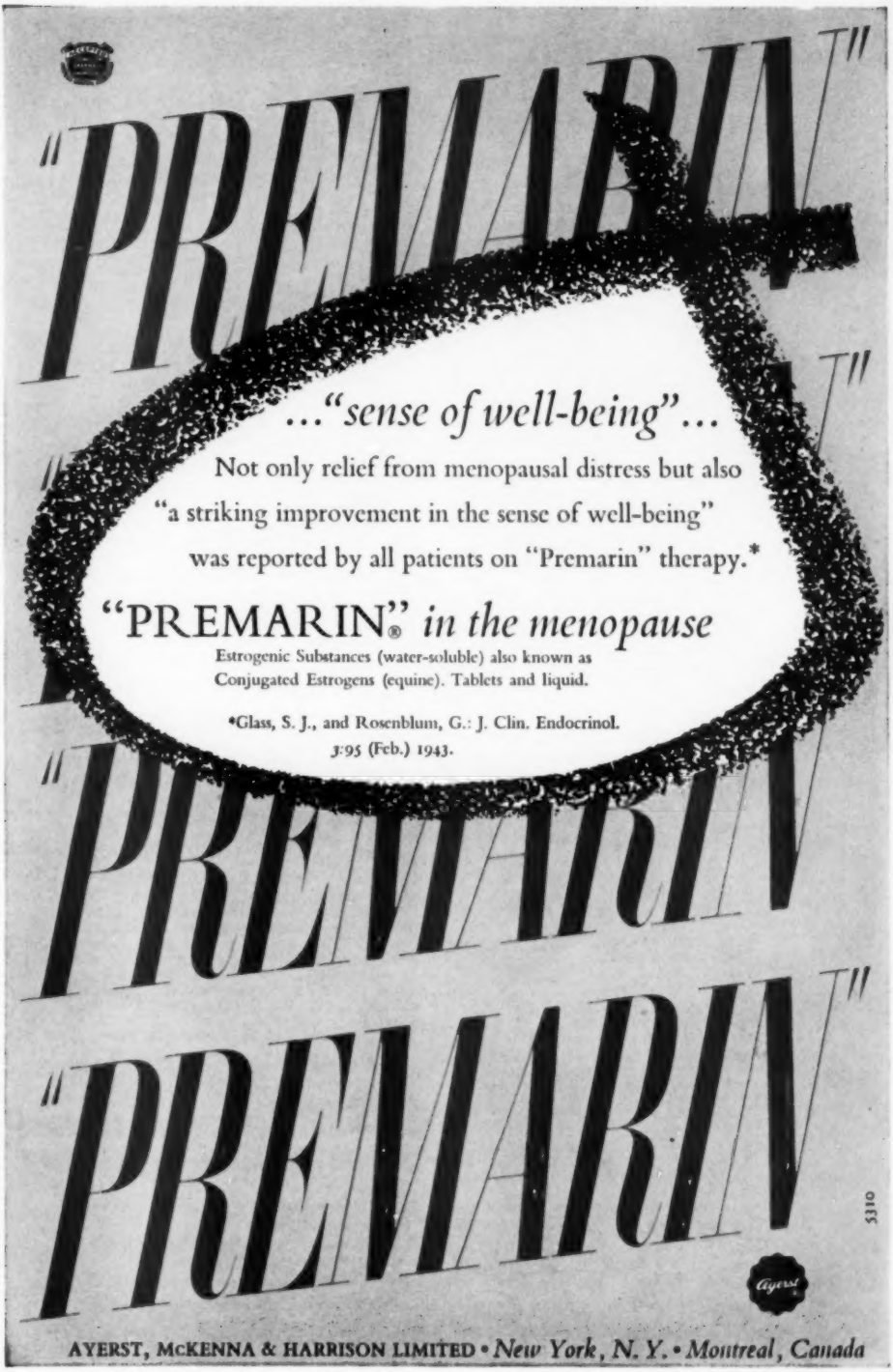
* *Leading gastroenterologists recommend:*

rest
sedation
antacids
nonirritating diet
anticholinergics

Ciba

1. Rogers, M. P., and Gray, C. L.: *Am. J. Digest. Dis.* 19:180, 1952.

2/ 1950M


"PREMARIN"
...“sense of well-being”...
Not only relief from menopausal distress but also
“a striking improvement in the sense of well-being”
was reported by all patients on “Premarin” therapy.*
“PREMARIN”® in the menopause
Estrogenic Substances (water-soluble) also known as
Conjugated Estrogens (equine). Tablets and liquid.
*Glass, S. J., and Rosenblum, G.: J. Clin. Endocrinol.
3:95 (Feb.) 1943.
5310
Ayerst
AYERST, McKENNA & HARRISON LIMITED • New York, N. Y. • Montreal, Canada

the ***most widely used***

ethical specialty for

care** of the **infant's skin

DESITIN®

OINTMENT

the pioneer external

cod liver oil therapy

Decisive studies[1,2] substantiate over 25 years of daily clinical use regarding the ability of Desitin Ointment to . . . . . *protect, soothe, dry and accelerate healing in...*

- **diaper rash** • **exanthema**
- **non-specific dermatoses**
- **intertrigo** • **prickly heat**
- **chafing** • **irritation**

(due to urine, excrement, chemicals or friction)

Desitin Ointment is a non-irritant blend of high grade, crude Norwegian cod liver oil (with its unsaturated fatty acids and high potency vitamins A and D in proper ratio for maximum efficacy), zinc oxide, talcum, petrolatum, and lanolin. Does not liquefy at body temperature and is not decomposed or washed away by secretions, exudate, urine or excrements. Dressings easily applied and painlessly removed.

Tubes of 1 oz., 2 oz., 4 oz., and 1 lb. jars

write for **samples** *and literature*

DESITIN CHEMICAL COMPANY

70 Ship Street • Providence 2, R. I.

1. Heimer, C. B., Grayzel, H. G. and Kramer, B.: Archives of Pediat. 68:382, 1951.
2. Behrman, H. T., Combes, F. C., Bobroff, A. and Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.

THESODATE

THE ORIGINAL ENTERIC-COATED TABLET
OF THEOBROMINE SODIUM ACETATE

provides
EFFECTIVE
WELL-TOLERATED
PROLONGED
VASO-DILATION

REPEATEDLY SHOWN and proven by objective tests on human subjects[1] – this is one of the most effective of all the commonly known Xanthine derivatives. Because of the enteric coating it may be used with marked freedom from the gastric distress characteristic of ordinary Xanthine therapy. Thus THESODATE, with its reasonable prescription price also, enjoys a greater patient acceptability.

Available: In bottles of 100, 500, 1000.

TABLETS THESODATE

*(7½ gr.) 0.5 Gm. (*3¾ gr.) 0.25 Gm.

THESODATE WITH PHENOBARBITAL

*(7½ gr.) 0.5 Gm. with (½ gr.) 30 mg.
(7½ gr.) 0.5 Gm. with (¼ gr.) 15 mg.
*(3¾ gr.) 0.25 Gm. with (¼ gr.) 15 mg.

THESODATE WITH POTASSIUM IODIDE

(5 gr.) 0.3 Gm. with (2 gr.) 0.12 Gm.

THESODATE, POTASSIUM IODIDE WITH PHENOBARBITAL

(5 gr.) 0.3 Gm., (2 gr.) 0.12 Gm. with (¼ gr.) 15 mg.

*In capsule form also, bottles of 25 and 100.

in
CORONARY ARTERY DISEASE

1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937
2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

For samples just send your Rx blank marked — 20TH6

Brewer
EST. 1852

BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.

Herald Square, N. Y.

Parkchester, Bronx

Jamaica, Queens

White Plains, N. Y.

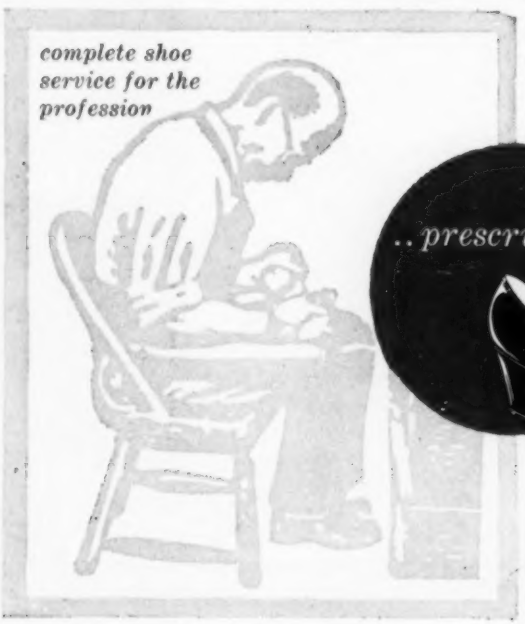
Flatbush, Brooklyn

MACY'S PRESCRIPTION DEPARTMENT

Macy's respects professional ethics. We carefully avoid discussing your prescription, either its ingredients or its use, with your patient. You can be assured that all your prescriptions are accurately compounded exactly as you write them. And all our preparations, made from the finest ingredients obtainable, are carefully checked by our supervising pharmacists.

No wonder so many physicians prefer Macy's Prescription Department.

complete shoe service for the profession



..prescribed with Confidence

Extensive selection of fine footwear for men, women and children.

•

A fully equipped, expertly staffed made-to-order department on the premises.

•

Distributors for MINOR'S "HOKE", Club Foot, Flat Foot and Straight Last Shoes.

Tarso-Supinator Tarso-Pronator Pre-Walkers

M. Braverman & Sons

1380 THIRD AVE., N. Y. C.

Bet. 78th & 79th Sts. TR 9-4410

Upjohn

superficial ophthalmic infections . . .

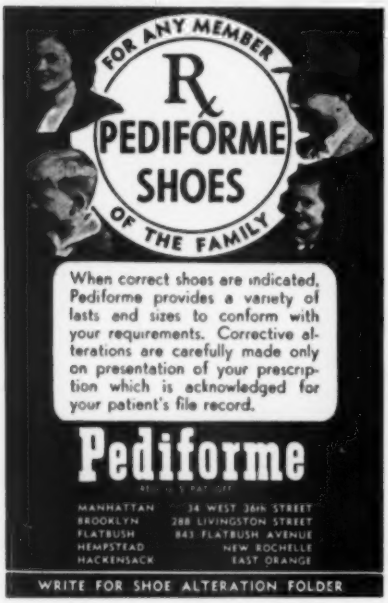
Myciguent 0.0.

Trademark Reg. U.S. Pat. Off.

Each drachm of ointment contains 5 mg. neomycin sulfate (equivalent to 3.5 mg. neomycin base)

Available in 1 drachm tubes

The Upjohn Company, Kalamazoo, Mich.


FOR ANY MEMBER
Rx
PEDIFORME
SHOES
OF THE FAMILY
When correct shoes are indicated, Pediforme provides a variety of lasts and sizes to conform with your requirements. Corrective alterations are carefully made only on presentation of your prescription which is acknowledged for your patient's file record.
Pediforme
MANHATTAN 34 WEST 36th STREET
BROOKLYN 288 LIVINGSTON STREET
FLATBUSH 843 FLATBUSH AVENUE
HEMPSTEAD NEW ROCHELLE
HACKENSACK EAST ORANGE
WRITE FOR SHOE ALTERATION FOLDER

NEW Book on Hypertension

PHEOCHROMOCYTOMA
and the
GENERAL PRACTITIONER

•

Joseph L. DeCourcy, M.D.
and
Cornelius B. DeCourcy, M.D.

Diagnosis of Pheochromocytoma Now Obligation of G.P.

"Pheochromocytoma, the chromaffin cell tumor of the adrenal medulla, should be considered in all cases of hypertension. . . . Emphasis must be placed on the clinical diagnosis, for up to the present it has been diagnosed principally post mortem."—Current Comment: J.A.M.A. 143:183,1950.

165 pp.—361 references $4.00

DeCourcy Clinic, Cincinnati 2, Ohio

THE TWENTY-SIXTH
GRADUATE FORTNIGHT OF THE
NEW YORK ACADEMY OF MEDICINE

2 East 103 Street New York 29, N. Y.

OCTOBER 19 TO 30, 1953

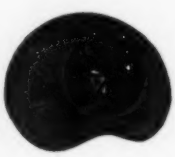
Subject:

DISORDERS OF THE BLOOD AND THE BLOOD-FORMING ORGANS

MAGER & GOUGELMAN, INC.

OVER A CENTURY OF SERVICE
1851 - 1953

PLASTIC AND GLASS EYES



- PRIVATE FITTINGS
- PERSONAL ATTENTION
- EXPERIENCE & SKILL

510 Madison Ave., N. Y. 22
Telephone PLaza 5-3756

Latest clinical report[1] demonstrates D&G

Aureomycin Packing is "far superior"

Breast abscess packed with Aureomycin Packing after incision and drainage.

Aureomycin Dressing

D&G Aureomycin Dressing helps hasten healing by controlling infection on skin graft sites, wounds, burns, rectal sites, etc. It is a close mesh 8" x 12" gauze liberally impregnated with a non-adherent base containing 2% aureomycin hydrochloride.

D&G Aureomycin Packing is a non-shed, double-selvage sterile gauze impregnated with crystalline aureomycin hydrochloride. Available in ½", 1" and 2" widths.

Request Aureomycin Packing and Aureomycin Dressing from the Surgical Supply Dealer who supplies your Davis & Geck sutures. Ask your nurses to keep these potent aureomycin aids in your treatment room. Your O.R. Supervisor has them now.

Now available—new film
"Aureomycin to Combat Local Infection"
—send requests to D & G Film Library

Recent investigators[1] state: "Aureomycin Packing is far superior to iodoform gauze, plain gauze or any other type of gauze packing known to us." They used it in abscesses and wound infections in which a variety of organisms was present. Plain sterile packing and iodoform packing were used as controls.

High, prolonged antibacterial action. After 16 hours, 65.4% of the aureomycin had been utilized, and after 48 hours, 93.3%. D&G Aureomycin Packing helps heal infected wounds *otherwise inaccessible to systemic antibiotics* because of thrombosed blood vessels and a total decrease in blood flow. "Foul odor was considerably reduced."[1]

No interference with healing. "Aureomycin and plain packing showed no impairment of growth of cells in tissue culture . . . . Iodoform showed decreased growth."[1]

Relatively non-toxic. "No significant local or systemic toxic effects were noted, nor was allergy or local skin irritation in evidence."[1]

[1]Marchisello, P. J., Prigot, Aaron, and Wright, L. T.: Am. Jour. Surg., Dec., 1952.

Davis & Geck, Inc.
A Unit of American Cyanamid Company

57 Willoughby Street, Brooklyn 1, N.Y.

CHARLES B. TOWNS HOSPITAL *Established 1901*

FOR THE TREATMENT OF ALCOHOLISM

NARCOTIC AND BARBITURATE

ADDICTIONS EXCLUSIVELY

Complete Medical & Psychiatric Treatment at predetermined cost. Privacy of patient is assured—if desired.

Literature on Request

Edward B. Towns, *Director*

293 Central Park West, N. Y. 24, N. Y.
SChuyler 4-0770

Member American Hospital Association

Aminophyllin . . .

a "most effective single agent for prompt relief" of severe **bronchial asthma**

"useful as a peripheral vasodilator and myocardial stimulant" in

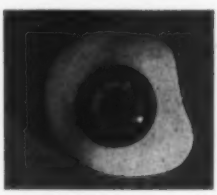
pulmonary edema
paroxysmal dyspnea
of congestive heart failure
Cheyne-Stokes respiration

H. E. DUBIN LABORATORIES, INC.
250 E. 43rd St. • New York 17, N.Y.

dubin
aminophyllin
(theophylline-ethylenediamine)

readily soluble for rapid therapeutic effect.

TABLETS • AMPULS
POWDER
SUPPOSITORIES



Satisfaction Guaranteed

Specialists in Plastic and Glass Artificial Human Eyes Exclusively

REFERRED CASES CAREFULLY ATTENDED

FRIED & KOHLER, Inc.

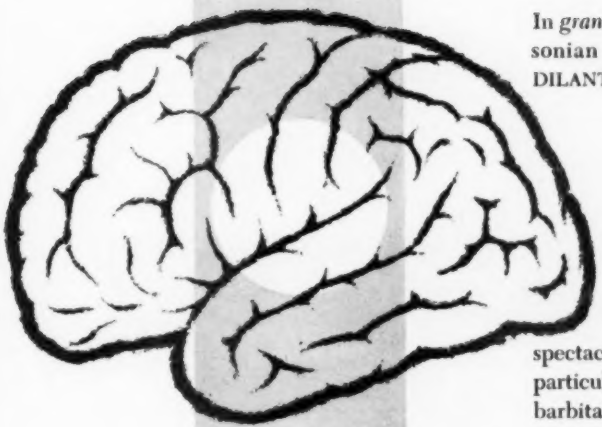
665 FIFTH AVENUE near 53rd Street — **NEW YORK, N. Y.** Tel. ELdorado 5-1970

No Finer Name in Contraceptives...

in the successful management of epilepsy...

DILANTIN®

a most effective and widely used anticonvulsant



In *grand mal*, psychomotor seizures, Jacksonian epilepsy and focal convulsions, DILANTIN is a therapy of choice.[1] It "offers the special advantage of . . . specificity for the motor cortex . . . without producing dullness of apprehension, lethargy, and lassitude. . . ."[2]

DILANTIN ". . . is particularly adapted for use in combination . . ."[3] and ". . . produces a spectacular result in *grand mal* attacks, particularly when combined with phenobarbital. . . ."[4]

DILANTIN Sodium (diphenylhydantoin sodium, Parke-Davis) is supplied in Kapseals® of 0.03 Gm. (½ gr.) and 0.1 Gm. (1½ gr.) in bottles of 100 and 1000.

(1) Krantz, J. C., and Carr, C. J.: The Pharmacologic Principles of Medical Practice, Baltimore, The Williams & Wilkins Company, 1949 (Reprinted 1950), p. 518. (2) *ibid*, p. 515. (3) Carter, S.: Epilepsy, in Conn, H. F.: Current Therapy 1952, Philadelphia, W. B. Saunders Company, 1952, p. 612. (4) Salter, W. T.: A Textbook of Pharmacology, Philadelphia, W. B. Saunders Company, 1952, p. 231.

Parke, Davis & Company

DETROIT, MICHIGAN

available on prescription only

Anti-asthmatic **Quadrinal tablets**

QUADRINAL TABLETS CONTAIN FOUR DRUGS, EACH SELECTED FOR ITS PARTICULAR EFFECT IN CHRONIC ASTHMA AND RELATED ALLERGIC RESPIRATORY CONDITIONS.

℞ ½ or 1 Quadrinal Tablet every 3 or 4 hours, not more than three tablets a day.

Each Quadrinal Tablet contains ephedrine hydrochloride ⅜ gr. (24 mg.), phenobarbital ⅜ gr. (24 mg.), Phyllicin (theophylline-calcium salicylate) 2 gr. (120 mg.), and potassium iodide 5 gr. (0.3 Gm.)

Quadrinal Tablets are marketed in bottles of 100, 500 and 1000.

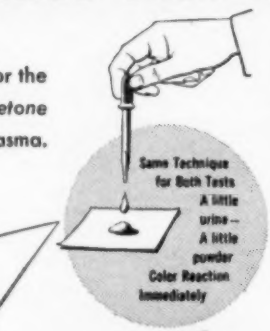
Quadrinal, Phyllicin, Trademarks E. Bilhuber, Inc.

distributor: BILHUBER-KNOLL CORP., *Orange, New Jersey, U. S. A.*

DENCO® SPOT TESTS

Acetone Test Denco for the rapid detection of *Acetone* in urine or in blood plasma.

Sugar Test Denco (Galatest Powder) for the rapid detection of *sugar* in urine.



ACETONE TEST DENCO

SUGAR TEST DENCO

COMBINATION KIT
For office — Medical Bag
Diabetic Patients

Write for descriptive literature:
THE DENVER CHEMICAL MFG. CO., INC. • Dept. 63C 163 Varick Street, New York 13, New York

NOW.. more efficient control of nausea and vomiting of . . .

PREGNANCY

MOTION SICKNESS

POST-ANESTHESIA

RADIATION SICKNESS

APOLAMINE®

Investigations prove that the antinausea drugs show a higher degree of effectiveness when given together.

Apolamine is a balanced combination of effective antinausea agents for a more comprehensive four-point control of nausea and the vomiting reflex.

APOLAMINE

CONTROLS THE CEREBRAL VOMITING CENTER
With a gentle sedation that depresses the vomiting reflex and relieves the patient's nervousness.

CONTROLS EXCESS PARASYMPATHETIC STIMULI
Which give rise to salivation, gastric hypersecretion and, in turn, vomiting.

HELPS TO CONTROL METABOLIC FUNCTIONAL IMBALANCES
Provides the vitamins of the B complex which tend to reduce the incidence of nausea and vomiting.

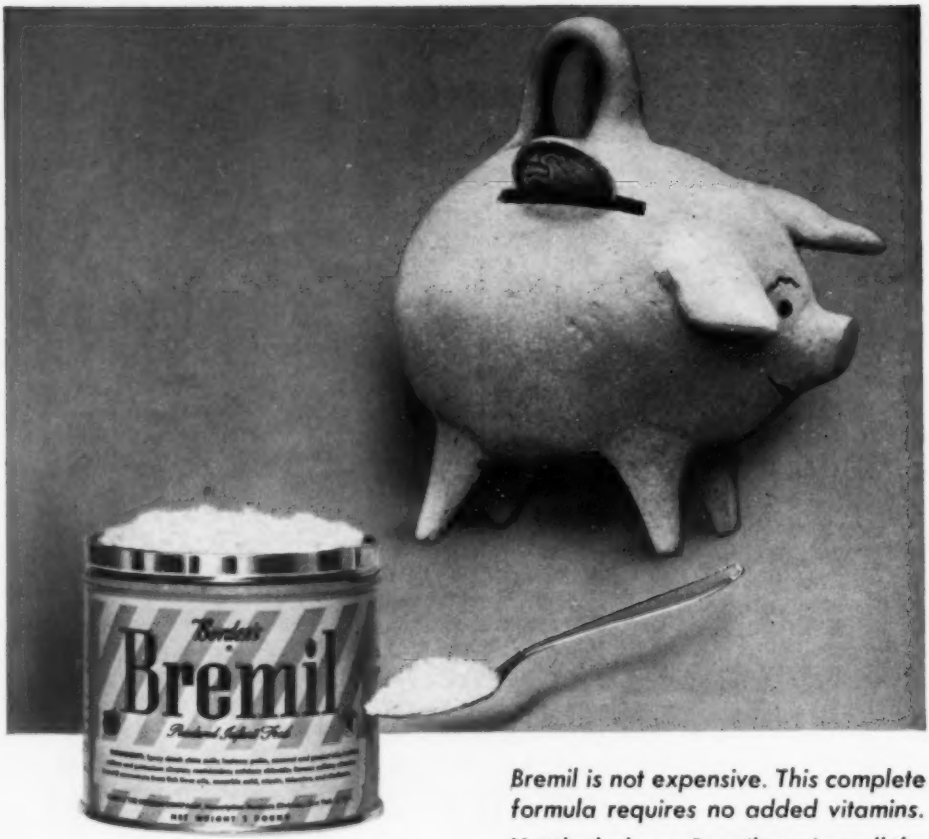
CONTROLS LOCAL GASTRIC IRRITATION
Minimizes the nauseous reaction to various foods by decreasing the sensitivity of the mucosal lining of the stomach.

Each tablet contains 15 mg. (1/4 grain) Luminal®, 0.1 mg. (1/600 grain) atropine sulfate, 0.2 mg. (1/300 grain) scopolamine hydrobromide, 0.1 Gm. (1 1/2 grains) benzocaine, 4 mg. riboflavin, 2.5 mg. pyridoxine HCl, and 25 mg. nicotinamide.

Apolamine is supplied in bottles of 100 tablets.

Winthrop-Stearns INC.
New York 18, N. Y. Windsor, Ont.

Luminal, trademark reg. U. S. & Canada, brand of phenobarbital



Costs no more per day than ordinary formulas requiring vitamin adjustment

Bremil is not expensive. This complete formula requires no added vitamins.

Yet the baby on Bremil receives all the known nutritional benefits of breast milk.

Bremil is a formula which approximates the milk of the mother:

. . . . in amino acid pattern
. . . . in fatty acid pattern
. . . . in carbohydrate (lactose)
. . . . in Ca:P ratio (1 ½ :1)
. . . . in curd-particle size
plus vitamin standardization

} **Bremil**

Bremil is the first and only infant food to achieve all of these requirements!

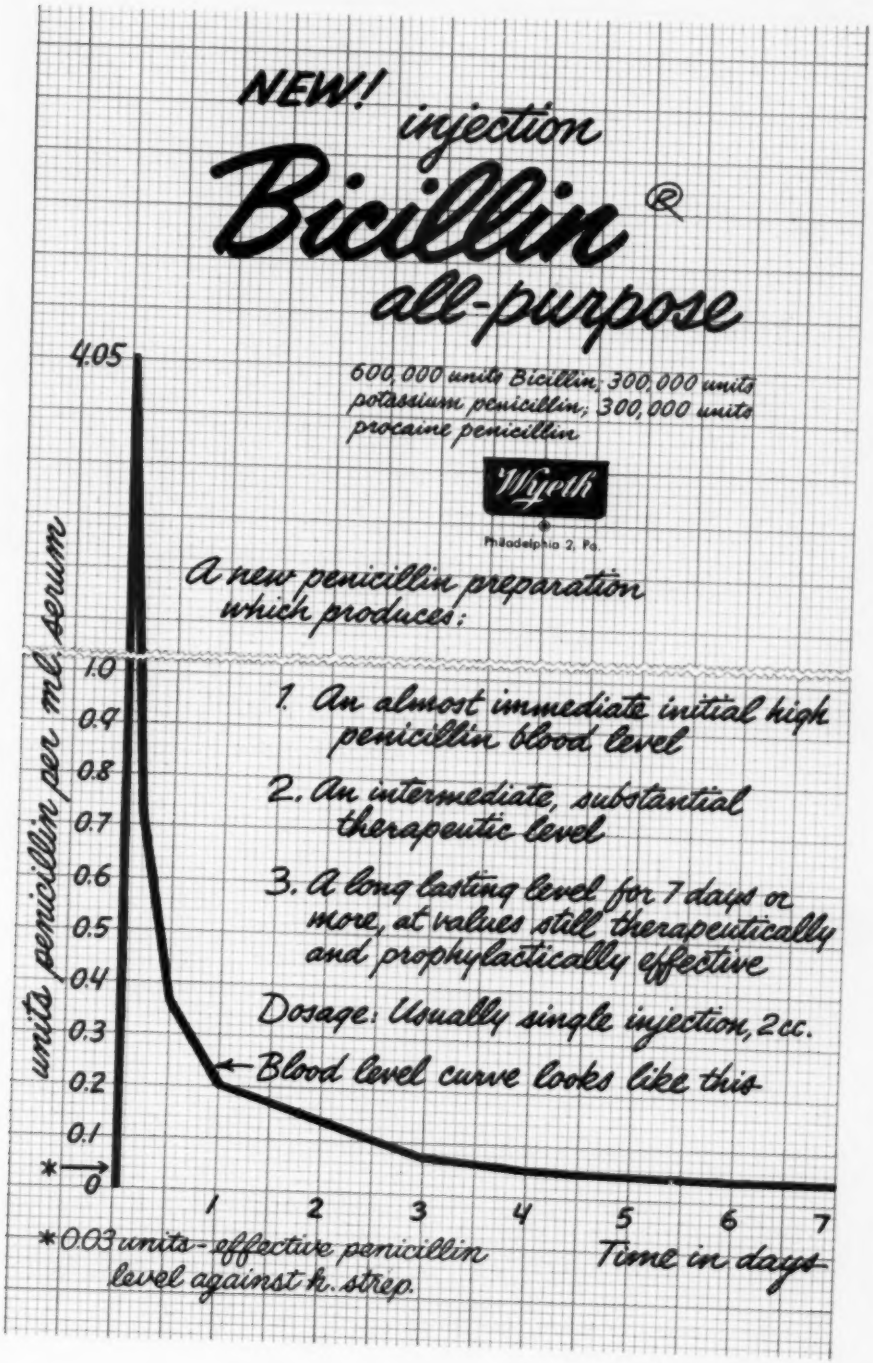
Prescribe Bremil for your babies who are not breast-fed . . . and compare their weight and growth gains during the important early months.

Clinical data and samples are available to you.

Write to:
PRESCRIPTION PRODUCTS DIVISION
The Borden Company, 350 Madison Ave., N. Y. 17

Bremil®

approximates the milk of the mother


NEW! injection
Bicillin®
all-purpose
600,000 units Bicillin, 300,000 units potassium penicillin, 300,000 units procaine penicillin
Wyeth
Philadelphia 2, Pa.
A new penicillin preparation which produces:
1. An almost immediate initial high penicillin blood level
2. An intermediate, substantial therapeutic level
3. A long lasting level for 7 days or more, at values still therapeutically and prophylactically effective
Dosage: Usually single injection, 2cc.
← Blood level curve looks like this
units penicillin per ml. serum
4.05
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
*
0
1
2
3
4
5
6
7
Time in days
*0.03 units-effective penicillin level against h. strep.

A New Surgical Bra

FOR YOUR MASTECTOMY PATIENTS

Trés Secréte RESTORATION*

inflatable bra

The distinct advantage of this entirely new surgical bra is its exclusive controlled-air-inflation principle that permits the addition of the precise amount of air necessary to fill out the figure. The complete absence of *pressure* and *irritation* makes it ever so comfortable . . . and *cool*.

How "RESTORATION" Restores the Figure

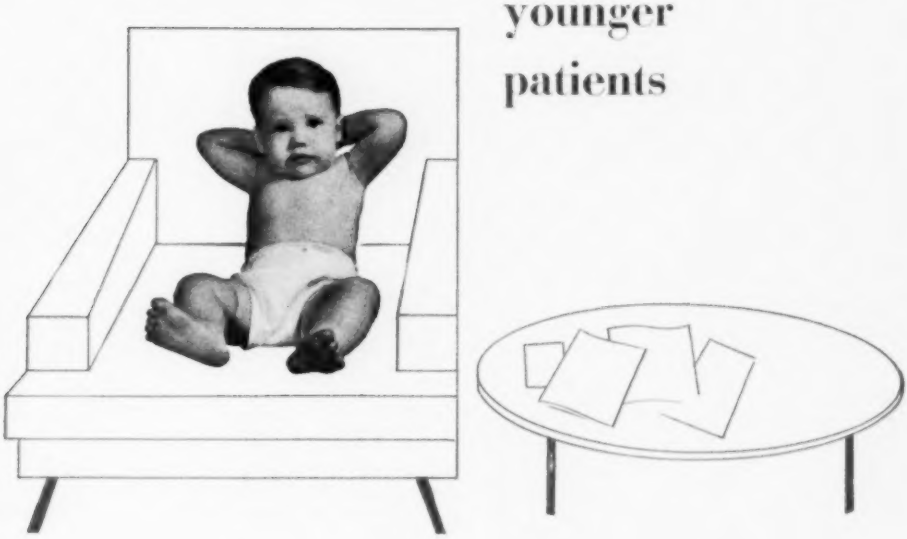
RESTORATION comes with pre-inflated inserts on which to make individual adjustments quickly and simply. Either one or both sides can be inflated or deflated for each personal problem. The inflatable insert extends all the way back under the arm so the figure is completely balanced.

In recommending the above, GLADYS GRAY, R.N., *again wishes to emphasize the advantages of her Registered Nurses organization in the kindly, sympathetic treatment and correct fitting so necessary for this type of patient. A phone call will bring you additional information on the product if desired.*

*Reg. U.S. Pat. Off. by La Resista Corset Co.

Gladys Gray R. N. 133 EAST FIFTY-EIGHTH STREET NEW YORK 22, N. Y.
SUITE 201 PLAZA 5-6328

New for your younger patients



CRYSTALLINE

Terramycin

BRAND OF OXYTETRACYCLINE AMPHOTERIC

FOR WELL-TOLERATED, PROMPTLY EFFECTIVE BROAD-SPECTRUM THERAPY

PEDIATRIC DROPS

1.0 GRAM

new economy in drop dosage treatment

Each bottle of Terramycin Pediatric Drops supplies 1.0 gram of Terramycin, often a sufficient total dose for therapy of many common illnesses.

delicious raspberry flavor

The same good taste which makes Terramycin Oral Suspension a favorite for older children and adults on broad-spectrum therapy.

new flexibility in infant dosage schedules

Nonalcoholic Terramycin Pediatric Drops supplies 100 mg. of pure crystalline Terramycin amphoteric in each cc. to meet most infant dosage requirements; may be diluted as required.

SUPPLIED:

10 cc. bottles containing 1.0 Gm. crystalline Terramycin amphoteric in raspberry-flavored, nonalcoholic vehicle with specially calibrated dropper.

Pfizer

world's largest producer of antibiotics

Antibiotic Division, CHAS. PFIZER & CO., INC., Brooklyn 6, N. Y.

oral diuretic without equal

"... superior ... in promoting sodium and water excretion."[1]

"... three-fourths the diuretic action of the standard [meralluride by injection] ..."[2]

"... a valuable substance to replace parenteral diuretics in patients who require continuous diuretic medication."[3]

NEOHYDRIN®

THE DIURETIC TABLETS THAT WORK

1. Moyer, J. H., and Handley, C. A.: Federation Proc. *11*:378, 1952.
2. Greiner, T.; Gold, H.; Warshaw, L.; Palumbo, F.; Weaver, J.; Mathes, S., and Marsh, R.: Federation Proc. *11*:352, 1952
3. Goldman, B. R., and Steigmann, F.: J. Lab. & Clin. Med. 40:803, 1952.

how to use this new drug

Maintenance of the edema-free state has been accomplished with as little as one or two NEOHYDRIN Tablets a day. Often this dosage of NEOHYDRIN will obtain per week an effect comparable to a weekly injection of MERCUHYDRIN.® When more intensive therapy is required one or two tablets three times daily may be prescribed as determined by the physician.

Gradual attainment of *intensive therapy* is recommended to preclude gastrointestinal upset which may occur in occasional patients with immediate high dosage. In rare instances a sensitivity to NEOHYDRIN may arise. Though sustained, the onset of NEOHYDRIN diuresis is gradual. Injections of MERCUHYDRIN will be initially necessary in acute severe decompensation.

Contraindicated in acute nephritis and nephrosclerosis.

Any patient receiving a diuretic should ingest daily a glass of orange juice or other supplementary source of potassium. Any patient receiving a diuretic should be watched for signs of depletion in sodium and chlorides especially in hot weather. Such depletion may first manifest itself as a refractivity to the diuretic and can be corrected by ingestion of sodium chloride.

packaging

Bottles of 50 tablets. There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea in each tablet.

...o resea...
..., MI... ...EE 1, WISCONSIN

Acetyl-p-aminophenol causes a marked rise in pain threshold within 30 minutes, with peak effect in about 3½ hours; maximum analgesia about 4 hours.

NEW ANALGESIC RAISES PAIN THRESHOLD 26%

Trigesic provides the advantages of acetyl-p-aminophenol, fast-acting analgesic, plus the benefits of aspirin and caffeine. Trigesic is an exceptional analgesic that has a three-fold action for the patient's comfort: analgesic, antipyretic, sedative. Bottles of 100 and 1,000.

TRIGESIC

Squibb Analgesic Compound

Per Tablet:

acetyl-p-aminophenol	0.125 Gm. (2 gr.)
aspirin	0.23 Gm. (3½ gr.)
caffeine	0.03 Gm. (½ gr.)

Trigesic with Codeine contains 8 mg. (⅛ gr.), 15 mg. (¼ gr.), 22 mg. (⅓ gr.) or 65 mg. (1 gr.) codeine phosphate.

'Trigesic' is a registered trademark

SQUIBB